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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

It is within the bounds of possibility that our readers may have noticed that the monthly issues of the *British Journal of Anaesthesia* are sometimes late in appearing. The observant may also have noticed, or at all events heard, that there has been a printers' strike on, and one moreover that lasted for seven weeks. We are in no way responsible for this but it has served to accentuate one of our besetting sins. It has been our policy to endeavour to produce as good a journal as we can and this has often meant delay which we prefer to printing "padding". Fortunately the *British Journal of Anaesthesia* has a world wide circulation and is contributed to by authors from many different countries; the submission to, and the returning from, such authors of the proofs of their articles is a time consuming business and makes its contribution to the lateness of our deliveries. We have had frequent interviews with our publishers in the past and we can assure our readers that it has been a matter of mutual concern constantly in our minds. Now that the strike is over we have been told that the parties to the dispute are now on better terms with each other, and this should lead to increased efficiency as well as increased harmony. We mention these matters not by way of excusing our own shortcomings of which we are very conscious but to shew our readers some of the difficulties with which we have to contend and so perchance to mitigate the severity of their criticisms. The excellent example of our contemporary in this matter of punctuality is constantly before our eyes and a spur to do better. It will obviously take us some time to catch up. We had planned to do this before the strike began but now it will of necessity be referred to a later date.

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A SIMPLE METHOD OF MEASURING THE COMPLIANCE AND THE NONELASTIC RESISTANCE OF THE CHEST DURING ANAESTHESIA

BY

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THE technique described in this paper utilizes simple equipment to measure compliance and airway resistance in the anaesthetized or paralyzed subject. Thus it allows a quantitative evaluation of the effects of disease, drugs and surgical stimuli. Knowledge of the mechanical properties of the chest is also wanted in the design and use of respirators.

EXAMPLE

Let us assume that at the end of expiration the airway of an anaesthetized patient is suddenly connected to a source of constant pressure, such as a spirometer bell on which a weight is resting, and that the pressure within that bell is 15 cm H_2O (above atmospheric.) Air will flow from the spirometer into the patient. If the descent of the spirometer bell is recorded on a kymograph, it produces a tracing such as that in figure 1, where volume is represented on the ordinate and time on the abscissa. In this example 900 ml of air has entered the subject at the time when flow ceases, i.e. the chest has had to be distended by the addition of 900 ml of air before exerting an elastic recoil equal to the pressure in the weighted spirometer bell (15 cm H_2O). The compliance of the chest is therefore 900/15, i.e. 60 ml/cm H_2O.

Now consider the point X on the record. At this point 600 ml of air has, so far, entered the lungs. The chest will exert a recoil pressure of 600/900 × 15, i.e. 10 cm H_2O. The pressure difference between the spirometer bell and the alveoli is therefore 15–10, i.e. 5 cm H_2O. At the point X, air is entering the subject at a rate of 1.2 l./sec (measured by the gradient of the curve at X). Thus 5 cm H_2O causes air to flow at 1.2 l./sec or, in other words, the resistance of the airway accounts for a pressure drop of 5 cm H_2O at a flow rate of 1.2 l./sec.

THEORY

When the chest (i.e. the lungs in the intact thorax) has been inflated above the resting respiratory level (RRL) a force must still be exerted to maintain the distension. This force opposes and equals the elastic recoil of the chest (P_{el}). It varies with the extent of the inflation, which is measured by the volume (V_T) of the additional gas which has entered the lungs. As more gas distends the lungs, the elastic recoil becomes stronger. Elastic recoil is measured by the pressure required to maintain an inflation while the respiratory muscles are relaxed. The elastic nature of the chest is usually expressed by the term "compliance" (C). In this method compliance of the chest

$$= \frac{\text{volume of gas forced into the lungs}}{\text{pressure holding the chest inflated}}$$

$$\text{i.e } C = V_T/P_{el} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Compliance varies with several factors, especially tissue characteristics and the size of the lungs. A reduction in compliance occurs, for example, in some types of pulmonary fibrosis,

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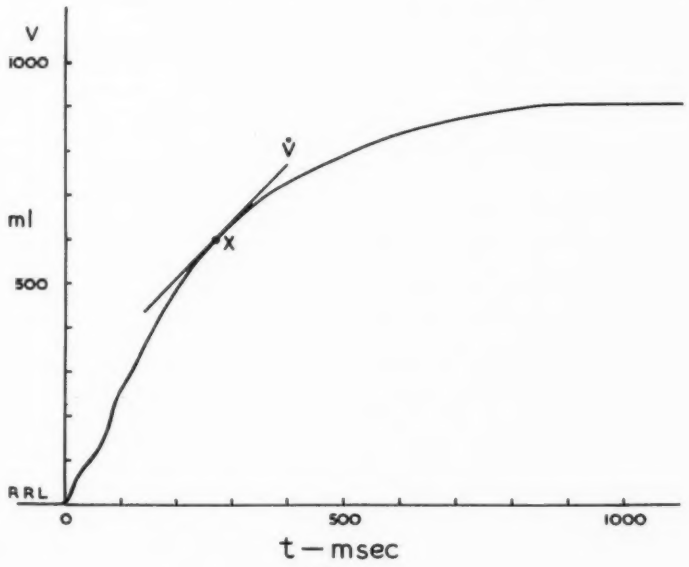

FIG. 1

Abscissa: time (t) in m.sec. Ordinate: volume of gas (V) in ml forced into the lungs by a constant pressure source. RRL=resting respiratory level. The tangent to the curve, drawn at X, has a gradient equal to the flow rate of gas at that moment.

because of increasing stiffness of lung tissue (i.e. the lungs are less compliant). A small compliance may, however, also be due to a reduced amount of functioning lung, since, to produce the same volume of inflation, less lung must be stretched to a greater extent, and to do this requires an increased pressure.

During the dynamic process of inflating the chest, the total force employed at any instant is greater than the force which would be required to maintain static distension at that particular lung volume. Thus, at any instant, the total inflating force (P) may be conveniently regarded as the sum of the two components, P_{el} and P_k, where P_{el} is the component opposed to "elastic" recoil and P_k is the additional force entailed by the actual process of inflating and may be considered as opposing "nonelastic" resistance. (For simplicity the directional attribute of force is here ignored and P_{el} is used for both elastic recoil and the equal force or pressure opposing it.) The total inflating force can be measured only when the respiratory muscles are relaxed, i.e. when the chest is inflated artificially. It is then measured by the difference between the pressure at the point where gases enter and the pressure around the chest (usually atmospheric pressure). By analogy with equation (1), the component opposed to elastic recoil equals V/C, where V is the volume of gas which has been introduced up to that instant. The component P_k, which specifies nonelastic resistance, is obtained by subtraction of the elastic component from the total inflating pressure (Rohrer, 1925): whence

$$P = P_{el} + P_k$$

or

$$P_k = P - P_{el}$$
$$= P - V/C \quad \ldots\ldots\ldots\ldots\ (2)$$

The component P_k, present only during flow, is related to the friction of air against the walls of the air passages and, to a lesser extent, the friction of the tissues as they slide to accommodate the inhaled air and expanding lungs. The greater the velocity with which gases flow into the

lungs, the greater are the frictional forces set up and therefore the greater is the pressure required to overcome them. The relation between pressure opposed to nonelastic resistance and volume flow rate of gas ($\dot{V}$) is not linear, but can be expressed numerically with sufficient accuracy by the expression:

$$P_k = k_1\dot{V} + k_2\dot{V}^2 \quad \ldots\ldots\ldots\ldots \quad (3)$$

where k_1 and k_2 are constants. Poiseuille's law is obeyed only at low flow rates (Brodie, 1954; McIlroy et al., 1955). Therefore, ordinarily, it is necessary to specify nonelastic resistance either by indicating the relationship between flow rate and pressure drop—as an equation or by means of a graph (e.g. fig. 2)—or simply by reporting the pressure loss corresponding to a given suitable flow rate (e.g. table I).

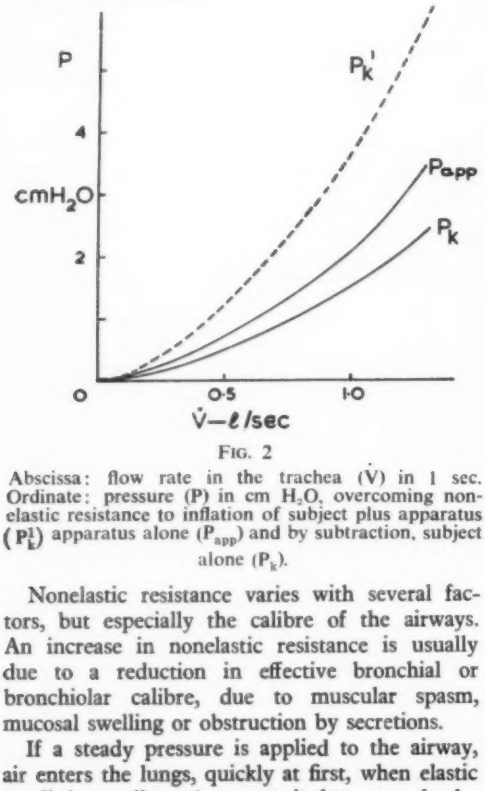

FIG. 2

Abscissa: flow rate in the trachea ($\dot{V}$) in 1 sec. Ordinate: pressure (P) in cm H_2O, overcoming nonelastic resistance to inflation of subject plus apparatus (P_k^1) apparatus alone (P_{app}) and by subtraction, subject alone (P_k).

Nonelastic resistance varies with several factors, but especially the calibre of the airways. An increase in nonelastic resistance is usually due to a reduction in effective bronchial or bronchiolar calibre, due to muscular spasm, mucosal swelling or obstruction by secretions.

If a steady pressure is applied to the airway, air enters the lungs, quickly at first, when elastic recoil is small, and progressively more slowly, as shown in figure 1. The origin in this figure corresponds to the RRL since the volume of inflation is always measured from this level. For a given constant pressure, the total volume of air which enters the lungs, V_T, depends essentially on the value of compliance (eqn. 1). But the shape of the volume-time curve is determined by the nonelastic resistance. If this is small, air rushes in readily and the curve is steep, but if the nonelastic resistance is high, gases enter slowly and the slope of the curve is reduced. The slope of the curve at any point represents the flow rate of air at the point of its entry into the subject.

As shown under "Example", the pressure drop attributed to nonelastic resistance at X is 5 cm H_2O. However, the apparatus itself is known to cause a pressure loss of 2.9 cm H_2O at this flow rate. Therefore the nonelastic resistance to inflation of the chest alone, at a flow rate of 1.2 l./sec, is overcome by $5.0 - 2.9 = 2.1$ cm H_2O. A series of values of P_k can thus be calculated and plotted against corresponding values of $\dot{V}$ and a curve of best fit drawn to display their relationship. Figure 2 shows such a curve, derived from the example in figure 1. (The constants k_1 and k_2 can then be calculated from the curve.)

The mathematical shape of the volume-time curve in figure 1 for a given inflating pressure is given by combining equations 2 and 3:

$$V/C + k_1\dot{V} + k_2\dot{V}^2 = P$$

In general, this equation specifies the magnitude of the pressure required for inflation of the chest in terms of compliance and nonelastic resistance and, for known pressures, specifies the resulting tidal volume and the time-pattern of its introduction.

During (passive) deflation of the relaxed chest, the force expelling air is provided by the elastic recoil of the chest. The elastic recoil is therefore opposed to the nonelastic resistance, whence

$$P_k = P_{el} = V/C$$

APPARATUS

The apparatus is shown diagramatically in figure 3. A constant pressure reservoir is formed by a standard 6-litre spirometer bell with a cross sectional area (in our model) of 208 sq. cm. A rod has been screwed vertically to the inside of its dome and carries at its lower end a piece of lead

TABLE I

The compliance and the nonelastic resistance of the chest below the larynx measured in eight subjects by the authors' method (inflation) and by the method of Comroe, Nisell and Nims (deflation).

	Compliance (ml/cm H_2O)		Pressure loss attributed to nonelastic resistance at 0.5 l./sec flow (to nearest 0.5 cm H_2O)	
Patient	Inflation	Deflation	Inflation	Deflation
1	55	68	0.5	1.5
2	41	57	0.5	1.5
3	36	53	0.5	0.5
4	42	32	1.5	2.5
5	24	37	3.0	4.0
6	40	–	2.5	–
7	45	–	1.0	–
8	44	–	3.0	–

weighing approximately 3.5 kg. This produces within the bell a pressure of 17 cm H_2O (above atmospheric) when the outlet is occluded. Alternatively a flat disc of lead may be rested on top of the bell, provided that it does not interfere with the suspension cord. The lead weight is made in several sections so that part or all may be used, thereby providing several different inflating pressures. It was found necessary to employ a spirometer bath with a narrow water jacket, leaving only about 0.5 cm clearances between the bath and the bell and between the bell and the spirometer core. This minimizes fluctuations in gas volume due to the oscillations of the water set up when air is allowed to escape suddenly from the weighted bell.

The spirometer outlet is connected by a length (about 1 metre) of wide-bore tubing (2.5 to 3 cm diameter) to a manually operated rapid-opening, wide-bore tap, for which purpose a Douglas bag tap or a 2-cm-bore gascock, well lubricated, is satisfactory. The other side of the tap is connected to a T junction, one arm of which communicates via a tap with the anaesthetic circuit; the other arm immediately joins the subject's special endotracheal tube connection. This connection presents minimal resistance to flow by virtue of being straight, wide-bored and bell-mouthed. The endotracheal tube should be short, as large as possible and should have a short cuff. The movement of the spirometer bell is recorded on a kymograph revolving at about 7 cm/sec.

PROCEDURE

The spirometer is calibrated and the pressures within the bell corresponding to given lead weights are measured under static conditions with a water manometer connected to the outlet.

The subject, lying supine, is anaesthetized in any convenient manner and the special endotracheal tube with its connection is inserted. Respiration is then slowed by a respiratory depressant drug or is abolished by hyperventilation or by the use of a muscle relaxant. At the end of an expiration, the subject's airway is opened to the atmosphere for one or two seconds, to ensure that the pressure in the airways is atmospheric, and it is then suddenly brought into communication with the weighted spirometer bell by manually operating the communicating tap, which is held in a suitable clamp. When the bell has come to rest, at the end of the inflation, the subject is allowed to expire into the room air or the anaesthetic apparatus by suitably turning the taps. The procedure is repeated several times and using several different inflating pressures.

The resistance of the spirometer and the connections to air flow was determined by substituting a large rigid drum of some 50 litres

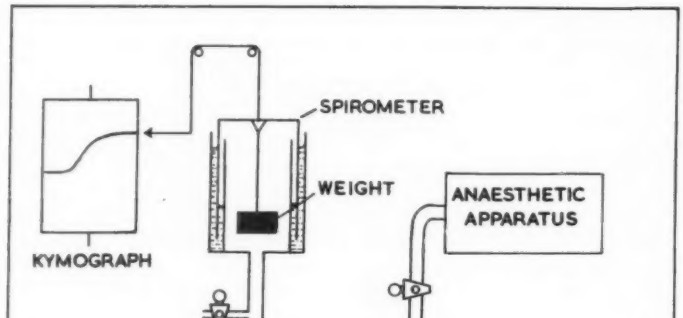

FIG. 3

Apparatus for inflating the chest from a constant pressure source and for recording continuously the volume of air which enters the lungs.

capacity for the subject and by proceeding as previously described. Such a drum provides a negligible flow resistance (due to orifice turbulence) so that the resistance calculated from this experiment is attributable entirely to the spirometer and connections. Such a determination of course, need be done only once for a given set of connections. The records are analyzed as explained under "Example". Gas volumes as recorded are at a pressure equivalent to P+ atmospheric pressure, and saturated with water at ambient temperature. They are corrected to BTPS. Errors due to gas exchange are negligible. The nonelastic resistance so determined does not include that of the airway above the trachea.

By removing the weight from the spirometer bell, the apparatus immediately becomes available for the estimation of compliance and nonelastic resistance of the chest during expiration by the method of Comroe, Nisell and Nims (1954). In this method the paralyzed chest is inflated, the airway pressure recorded and then the subject is permitted to exhale into a spirometer. The expiratory spirogram is analyzed by using the formula $P_k' = V/C$, where P_k' is the pressure drop opposed to nonelastic resistance of subject and apparatus.

ACCURACY

Before considering the accuracy of the method, three assumptions require discussion.

(1) It has been assumed that the inspiratory muscles are inactive during inflation. This need not be considered further when relaxants are employed. In a number of cases we have estimated the mechanical properties of the chest with this method in anaesthetized and paralyzed subjects and we have repeated the measurements when the paralysis has passed. Generally there has been no change in the records so obtained, but on occasions the sudden application of pressure to the airway elicited a spontaneous inspiration, apparent on the record as a considerable increase in the volume of inflation. Although not seen in our subjects, breath holding or even expiratory effort may be elicited by a sudden increase of airway pressure during light anaesthesia. When relaxants are not used it is therefore advisable to

make a number of measurements, using deep anaesthesia, and to watch for muscular activity by the subject.

(2) It has been implied that the inflation pressure produced by the weighted spirometer bell remains constant. This is not so: when the tap is suddenly opened, air escapes more rapidly than the spirometer bell can descend. A number of experiments were performed in which the pressure within the bell was recorded with a rapid-response electromanometer while "inflations" of a patient "analogue" were made. The analogue consisted of a 50-litre rigid drum with adjustable tubular inlet. The experiments demonstrated that on first opening the tap the pressure within the bell falls momentarily and then fluctuates with diminishing amplitude about the value at rest, as shown in figure 4. The pressure generally settles to within 1 cm H_2O of the final (static) value within 350 m.sec. The pressure oscillations correspond to the wavelike commencing portion of the spirometer tracing shown in figure 1. It is therefore possible to decide from the spirometer record how much of its earlier portion has to be excluded from analysis. This varies, but usually amounts to the first 200 to 400 m.sec.

(3) It has been assumed that the dimensions of the apparatus remain constant. This is true only after the tap has been fully opened. The time taken to achieve this has been measured with an electric counter and, though varying with the skill of the operator and the lubrication of the tap, it can usually be kept to less than 100 m.sec, a period less than that which must be neglected because of fluctuations in the inflating pressure.

Rather than investigate each error individually, the accuracy of the method was checked by using it to measure the "compliance" of the patient analogue and by using the method to measure the resistance to flow of two brass tubes in series with the analogue and comparing the results with those obtained by the standard method of measuring flow resistance with steady flows. In twenty successive estimations of the compliance of the drum, the coefficient of variation was less than 2 per cent. The two tubular objects had flow resistances causing, respectively, 1.3 and 5.8 cm H_2O loss of pressure head at 0.8 l./sec. Determinations using the method described agreed with these values to within 0.3 cm H_2O. It is considered that this level of absolute accuracy is adequate for the purpose under consideration.

SENSITIVITY

The least additional resistance which can be detected by this method depends on the total flow resistance of the circuit. It is essential to keep

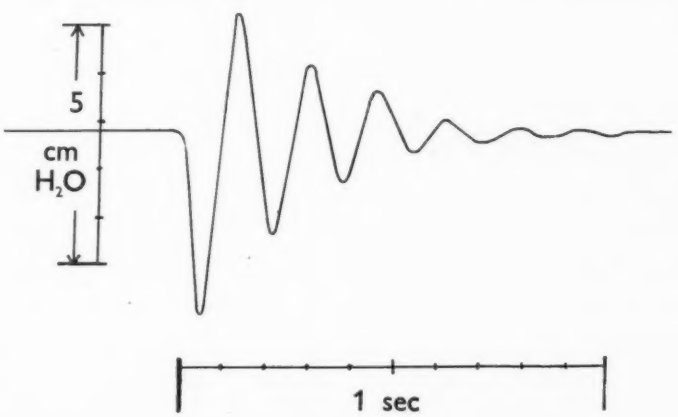

FIG. 4

Pressure oscillations inside the weighted spirometer bell when the outlet is suddenly opened. Zero pressure (not shown) is below the tracing.

the resistance of all connections, including endotracheal tubes, as low as possible. In particular, right-angled connections should be avoided. If the resistance of the apparatus is high, small variations in the nonelastic resistance of the subject will not be detected. In experiments with the patient analogue it was possible to detect added resistance of 1.5 cm H_2O at 1 l./sec. The clinical detection of an increase in resistance is unlikely at less than three or four times this value.

SPECIMEN RESULTS

In table I we present some specimen results obtained from healthy adults. "Inflation" refers to the use of the weighted spirometer bell and "deflation" to the technique of permitting passive expirations into the spirometer, Comroe, Nisell and Nims (1954). In these subjects inflation pressures, using the weighted spirometer, were 10 or 15 cm H_2O. Deflation was permitted from initial airway pressures ranging from 10 to 22 cm H_2O. The figures are the means of a large number of estimations whose coefficients of variation are less than 20 per cent. The differences between results obtained by the two methods are significant ($P<0.01$). In the calculations it was assumed that compliance does not vary during the estimation. The nonelastic resistance of the chest is measured from below the endotracheal tube. Volumes were not corrected to BTPS.

DISCUSSION

The technique we have described is complementary to the method of Comroe, Nisell and Nims (1954). It is important to appreciate that a technique of measurement may influence the values which are obtained with it. The method of Comroe, Nisell and Nims employs, of necessity, an interval of breath holding whilst the airway pressure is recorded. However, it has been shown by a number of workers (Cherniack, Adamson and Hildes, 1955; Butler, 1957) that compliance increases with the duration of pulmonary distension. In our technique inflation is brief, rarely lasting for more than 1.5 seconds. This may explain why, except for patient 4, compliance was less when measured from inflation than from deflation. As it is rather uncommon for the chest to be held inflated during spontaneous or artificial respiration, the values obtained by our method are of greater clinical use. In particular, they represent values applicable to patterns of inflation which involve step changes in airway pressure, such as occur, for example, with use of the "Radcliffe" respirator and the "Pneumotron".

Compliance is also influenced by other factors, especially tissue characteristics (Hammond, 1957) and total lung capacity (Marshall, 1957). It is therefore not proposed to analyze the specimen results in detail in this paper, but only to point out that they are, broadly, in agreement with other reported values for the compliance of the chest during anaesthesia (Nims, Conner and Comroe, 1955; Wu, Miller and Luhn, 1956; Howell and Peckett, 1957; Butler and Smith, 1957; Foster, Heaf and Semple, 1957; Bromage, 1958; Sechzer, 1958).

Nonelastic resistance also varies with the method of its estimation. Firstly, the nonelastic resistance of the chest, calculated from equation 2, depends on the value for compliance. If compliance is overestimated, the nonelastic resistance will also be given an incorrect value. We have assumed that compliance remains constant during any inflation. This assumption, based on the work of Howell and Peckett (1957) and others, can easily be tested by using a number of different inflation pressures.

Secondly, the method used may affect the calibre of the airways. It has been shown by Shepard et al. (1957) and by Briscoe and DuBois (1958) that the small airways are as distensible as the lungs and that therefore nonelastic resistance varies in an inverse fashion with lung volume. In this technique the highest flow rates occur when the lungs are near the resting respiratory level (RRL), small flow rates when the lungs, including the small airways, are distended. In the method of Comroe, Nisell and Nims these relations are reversed. Moreover, when the pressure difference producing deflation is large, as at the beginning of a passive expiration, partial collapse of airways may occur (Campbell, Martin and Riley, 1957; Dekker, Defares and Heemstra, 1958), thus further raising nonelastic resistance. On the other hand, resistance to inflation near the RRL may be caused in part by surface tension holding alveolar walls together. Again, the values

for nonelastic resistance obtained by our technique are applicable especially to inflation by an abrupt increase in airway pressure; higher values would be expected during deflation. This is illustrated by our results. Our values are much lower than those reported by others (Wu, Miller and Luhn, 1956; Sechzer, 1958) and it is possible that their high values resulted from differences in anaesthetic technique which predisposed to narrowing of airways.

SUMMARY

A method is described for measuring the compliance and nonelastic resistance of the chest during anaesthesia, using simple equipment. The method employs a weighted spirometer bell as a source of approximately constant pressure. The bell is suddenly brought into communication with the airway of a paralyzed or temporarily apnoeic subject. Descent of the bell is recorded on a rapid kymograph and measures the volume of air which has entered the subject's lungs at any moment. The compliance and the nonelastic resistance of the chest to inflation are readily derived from such a tracing. The method is accurate to 0.3 cm H_2O for resistance and to 2 per cent for compliance in tests with a mechanical patient analogue. Specimen results are reported.

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THE DIAGNOSIS OF NEUROMUSCULAR BLOCK IN MAN*

BY

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IN the past neuromuscular blocking drugs have been regarded as acting at the motor endplate either by depolarization (like acetylcholine) or by nondepolarization (like d-tubocurarine). This simple classification became widely accepted. Nevertheless, the actions of some newly discovered relaxant drugs have cast doubts on this simple classification and it has been suggested that they show characteristics of both types of neuromuscular block. Furthermore, confusion has arisen from the suggestion that suxamethonium (a depolarizing drug) may actually alter its mode of action—so that after repeated doses it produces a nondepolarizing type of neuromuscular block.

Clinically, if muscle relaxants are used, it is extremely important to determine the precise type of neuromuscular block that is present. Thus, a nondepolarizing block can be reversed rapidly by an anticholinesterase drug (e.g. neostigmine) whereas a depolarizing block is merely potentiated.

Unfortunately, in man there is very little data upon the state of neuromuscular transmission in the presence of the various muscle relaxants. Almost all the available evidence is based upon animal studies. An attempt has therefore been made to measure changes in neuromuscular transmission in anaesthetized patients under the influence of the principal muscle relaxants.

METHOD

Subjects undergoing routine surgical operations requiring the use of a muscle relaxant in the course of the anaesthetic technique were chosen at random. Each patient was premedicated with papaveretum (10 mg) and hyoscine (0.45 mg): induction of anaesthesia was with 500 to 750 mg of thiopentone and maintained with nitrous oxide-oxygen (6:2 l./min) given in a semiclosed circuit. Intermittent doses of pethidine hydrochloride (totalling 20–80 mg) were given as required.

Neuromuscular transmission was measured by a modification of the method described by Harvey and Masland (1941). A supramaximal stimulus of 0.2 milliseconds duration was administered through a needle electrode in the region of the ulnar nerve at the elbow. An earth lead was firmly attached over the forearm. Surface recording electrodes were applied over the muscle mass of the abductor digiti minimi. The hand and forearm were firmly attached to a back-splint to prevent movement.

The portable electromyograph was capable of delivering a stimulus at rates of 1, 2.5, 10, 25 and 50 per second. The design also included a device enabling single twitch stimuli to be administered automatically at varying intervals before and after a train of tetanic stimulations.

The following features were specifically studied:

(1) The ability of muscle to respond to varying rates of stimulation in the presence of neuromuscular blocking drugs.
(2) The presence or absence of post-tetanic facilitation. (This is signified by an increase in the height of a single action potential delivered 1–5 seconds after a burst of tetanic stimulation as compared with a single control stimulus delivered beforehand.)
(3) The effect of anticholinesterase drugs upon the neuromuscular block.

The following drugs were studied:

(1) Decamethonium iodide.
(2) Suxamethonium chloride.
(3) d-Tubocurarine chloride.
(4) Gallamine triethiodide.

*Based on a paper read at the Scientific Meeting of the Faculty of Anaesthetists on May 2, 1959.

Edrophonium and neostigmine were used for anticholinesterase therapy. Whenever neostigmine was used it was always preceded by the intravenous injection of 1 mg atropine sulphate. There was no evidence that atropine alone affected neuromuscular transmission.

In each case an intravenous dose of the muscle relaxant sufficient to produce complete neuromuscular block of the hypothenar muscles was administered and the various effects upon the neuromuscular block were studied during the recovery.

Preliminary studies established that the basic anaesthetic technique (including the intravenous administration of pethidine hydrochloride) did not influence neuromuscular transmission even when continued for 2 hours or more. In the anaesthetized patient the effects of a single dose of d-tubocurarine or gallamine could readily be differentiated from a similar dose of either suxamethonium or decamethonium.

RESULTS

(a) *Decamethonium.*

The most characteristic feature of this type of neuromuscular block is the ability of the motor endplate to transmit successive stimuli even when very fast rates of stimulation are used (figs. 1A, B, C, D).

In the example shown in figure 1 the degree of paresis is approximately 50–80 per cent. The action potential is well maintained for short periods even with a rate of stimulation rising to 50 per second. At this fast rate signs of fatigue and ischaemia of the muscle fibre are responsible for a gradual failure of the action potential after some 30 seconds or more of repeated nerve stimulation.

There was no evidence of post-tetanic facilitation after a period of tetanic stimulation. (This is not shown in the figure.)

The findings following a single dose of suxamethonium were indistinguishable from those after decamethonium.

BEFORE DECAMETHONIUM

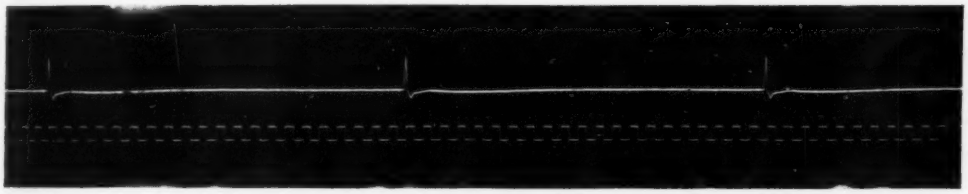

FIG. 1A
Rate of nerve stimulation: 2.5 per second

FIG. 1B
Rate of nerve stimulation: 25 per second

AFTER 2 MG DECAMETHONIUM

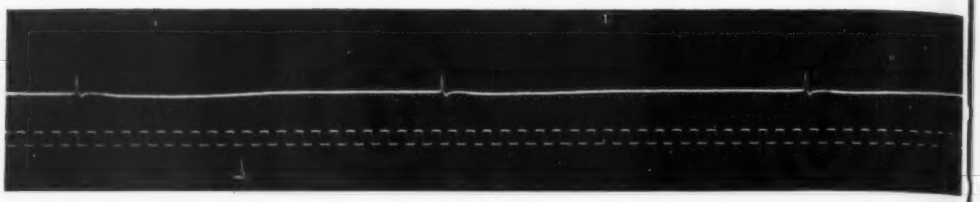

FIG. 1C
Rate of nerve stimulation: 2.5 per second

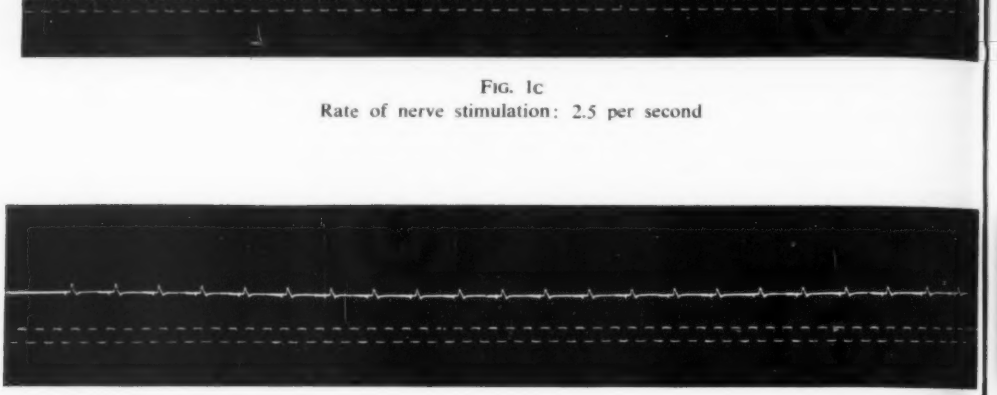

FIG. 1D
Rate of nerve stimulation: 25 per second

Neostigmine in the presence of a depolarization block.

The effect on the already existing decamethonium block (fig. 1D) of the injection of an anticholinesterase drug (2.5 mg. neostigmine) is illustrated in figure 1E.

In this instance the neostigmine was given during the recovery phase of the decamethonium block and it can be clearly seen that it produced a progressive failure of neuromuscular transmission with rapid rates of stimulation. Slow or twitch rates of stimulation were unaffected by the neostigmine. The significance of these changes can best be understood by reference to the effects of anticholinesterase drugs alone (see figs. 3 and 4).

2.5 mg neostigmine after 2.0 mg decamethonium

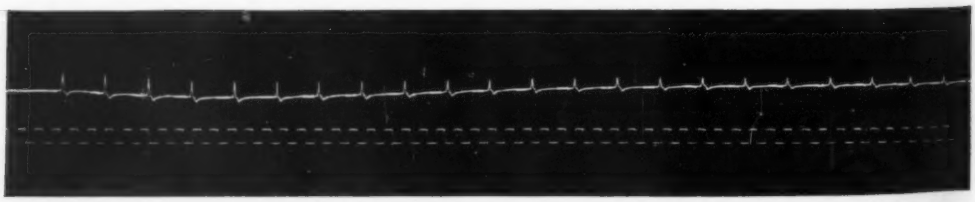

FIG. 1E
Rate of nerve stimulation: 25 per second

(b) *d-Tubocurarine.*

In direct contrast to decamethonium, the principal feature of this type of neuromuscular block is an inability to maintain successive stimuli (figs. 2A, B, C, D).

The major proportion of this decrement takes place in the first three or four stimuli of the train, and only a very small fall is distinguishable in the remainder until finally a potential of considerably reduced amplitude is steadily maintained. This progressive failure of neuromuscular transmission can be observed with both fast and slow rates of stimulation. In man, unless the interval between successive twitch stimuli is at least 3–5 seconds, some decrement after successive stimuli will be observed.

After a train of tetanic stimuli lasting 5 to 10 seconds or longer post-tetanic facilitation is observed. The longer the duration of tetanic stimulation, the more likely facilitation is to be present: the ideal interval between the end of the tetanus and the delivery of a single twitch is 2–4 seconds.

The results with gallamine triethiodide were identical and indistinguishable from those with d-tubocurarine.

BEFORE D-TUBOCURARINE

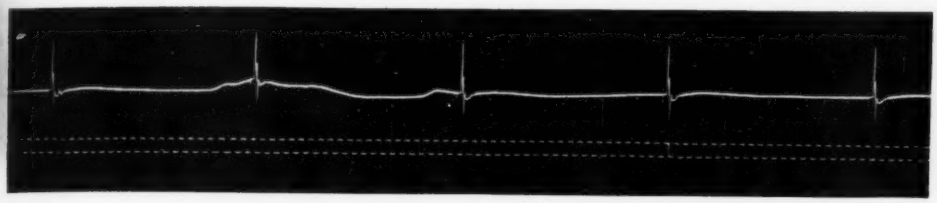

FIG. 2A
Rate of nerve stimulation: 2.5 per second

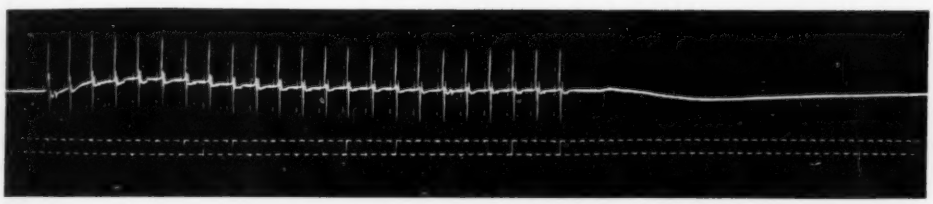

FIG. 2B
Rate of nerve stimulation: 25 per second

AFTER 15 MG D-TUBOCURARINE

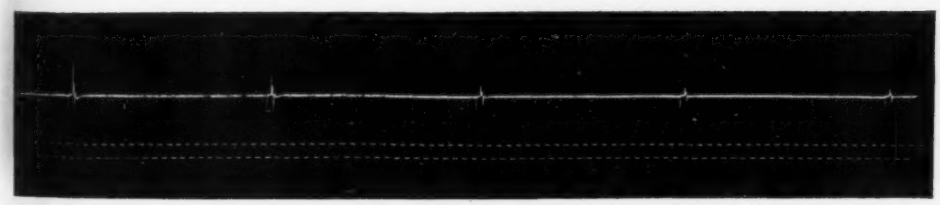

FIG. 2C
Rate of nerve stimulation: 2.5 per second

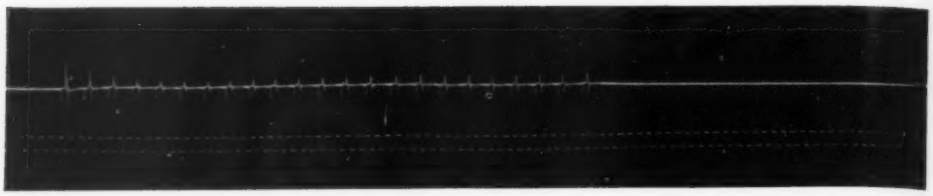

FIG. 2D
Rate of nerve stimulation: 25 per second

Neostigmine in the presence of a nondepolarization block.

Within 2 minutes of the administration of 2.5 mg of neostigmine in the presence of either a d-tubocurarine or a gallamine block, the rapid failure or decrement of successive stimuli started to disappear (fig. 2E). By the fourth minute the height of the single potential had shown a considerable increase over the previous value and the neuromuscular junction could now often transmit fast rates of stimulation without showing any decrement at all. If large doses of d-tubocurarine (such as 25–30 mg) had been used, the return to the control value was considerably delayed.

From these observations it was evident that the administration of neostigmine (2.5 mg) in the presence of an existing neuromuscular block provided a useful method of diagnosis of the precise mechanism underlying that block.

After neostigmine

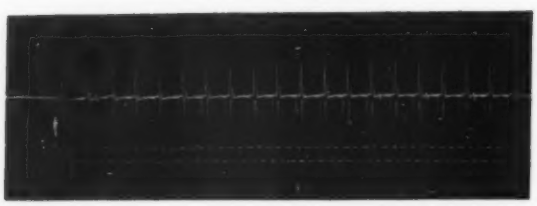

FIG. 2E
Rate of nerve stimulation: 25 per second

Neostigmine alone.

The finding that neostigmine produced changes of a different nature in the presence of either a depolarization or a nondepolarization block made it necessary to study the effect of an injection of neostigmine alone.

Under the same conditions, therefore, a group of patients were given doses of neostigmine ranging from 1.25 mg to 5 mg preceded by 1 mg of atropine sulphate. Two distinct phases of response—related to the dose level—could be recognized.

(1) Following moderate doses (1.25–2.5 mg) a failure to maintain fast tetanic rates of stimulation was observed (figs. 3A, B, C, D, E, F). At first it was only visible at rates of 50 per second (figs. 3E, F), but increasing the dose led to its appearance at 25 per second (figs. 3C, D), then at 10 per second, and finally even at 5 per second. It was not observed at 2.5 per second even when a dose level of 5 mg of neostigmine was used.

Unlike the decrement produced by d-tubocurarine, in this instance a further dose of neostigmine leads to a worsening of the condition. This phenomenon could be explained upon the basis of accumulation of acetylcholine at the neuromuscular junction.

(2) Following large doses of neostigmine (2.5–5 mg) a persistent degree of neuromuscular block can be recognized even at very slow rates of stimulation (figs. 4A, B). As will be seen in figure 4B the action potential is reduced in height, signifying neuromuscular block similar to that produced by decamethonium. This may be due to a direct depolarizing action of neostigmine upon the motor endplate.

(1) Moderate dose of neostigmine

Before neostigmine

FIG. 3A
Rate of nerve stimulation: 2.5 per second

After neostigmine

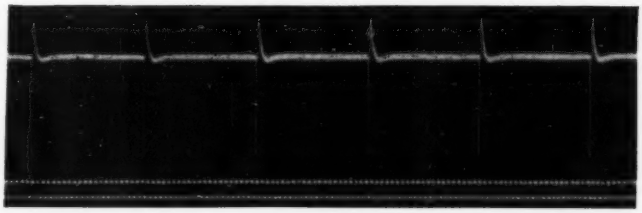

FIG. 3B
Rate of nerve stimulation: 2.5 per second

Before neostigmine

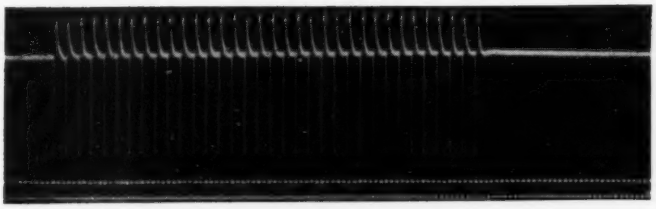

FIG. 3C
Rate of nerve stimulation: 25 per second

After neostigmine

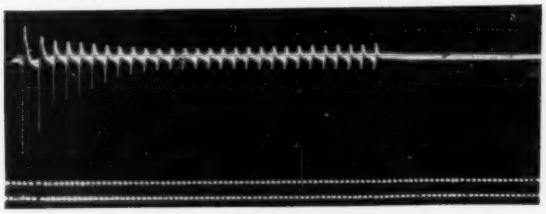

FIG. 3D
Rate of nerve stimulation: 25 per second

Before neostigmine

FIG. 3E
Rate of nerve stimulation: 50 per second

After neostigmine

FIG. 3F
Rate of nerve stimulation: 50 per second

(2) Large dose of neostigmine

Before neostigmine

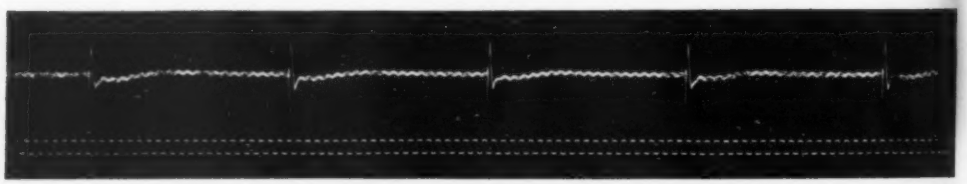

FIG. 4A
Rate of nerve stimulation: 2.5 per second

After neostigmine

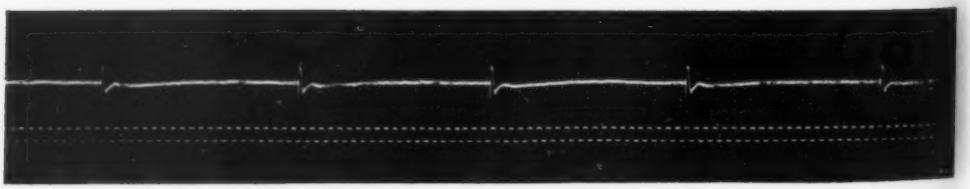

FIG. 4B
Rate of nerve stimulation: 2.5 per second

Effect of continuous infusion of suxamethonium on neuromuscular transmission.

Following a single dose of suxamethonium (50 mg) the pattern of the neuromuscular block is clearly of the depolarization type (figs. 5A, B). Thus, the action potentials are well maintained even with fast rates of stimulation and there is no post-tetanic facilitation. Edrophonium potentiates the neuromuscular block.

If, however, the patient receives a continuous infusion of suxamethonium the pattern of the neuromuscular block gradually changes as the total dose increases. By the time a dose of 500–1,500 mg has been reached the characteristic fade in the series of action potentials—normally associated with a nondepolarizing (d-tubocurarine) block—can be clearly seen (fig. 5C).

This type of response occurred consistently in seven patients investigated. The larger the dosage used, the more obvious becomes the decrement of repeated potentials.

The effect of neostigmine on this response was also studied. Within 2 minutes of the intravenous injection of 2.5 mg the fade in the action potential started to disappear and by the fifth minute was practically negligible (fig. 5D). At the same time the height of each single potential increased, denoting a lessening of the neuromuscular block.

These results suggest that not only does neostigmine fail to potentiate the late block of suxamethonium but also that it may actually reverse it. Great caution, however, must be exercised in interpreting these results, since suitable allowance must also be made for the normal recovery of the underlying neuromuscular block due to the help of the destruction of suxamethonium by plasma cholinesterase. Alternatively, any change in the neuromuscular block might be due to a breakdown product of suxamethonium, as, for example, the monocholine derivative.

The final proof of the effect of neostigmine on the late block produced by a depolarizing drug could only be obtained by a study of its action in the presence of large doses of decamethonium, as this drug is believed to be excreted unchanged in the urine.

Before suxamethonium

FIG. 5A
Rate of nerve stimulation: 2.5 per second

After 50 mg suxamethonium (during recovery)

FIG. 5B
Rate of nerve stimulation: 2.5 per second

After 1.500 mg suxamethonium

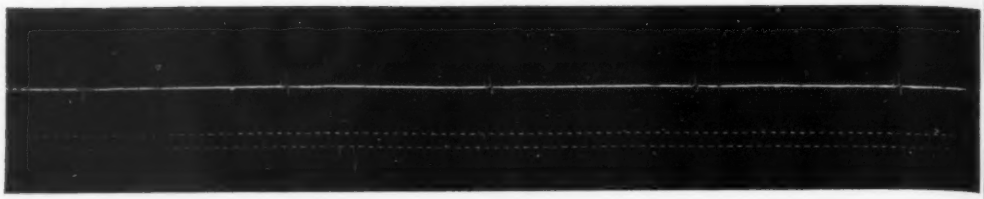

FIG. 5C
Rate of nerve stimulation: 2.5 per second

After 2.5 mg neostigmine following 1.500 mg suxamethonium

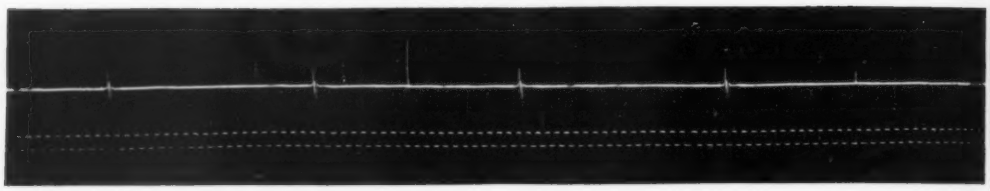

FIG. 5D
Rate of nerve stimulation: 2.5 per second

Neostigmine and the late block of decamethonium.

Just as it had been possible to demonstrate a change in the characteristics of neuromuscular block following the infusion of large doses of suxamethonium, so repeated intermittent doses of decamethonium led to a similar result.

After a single dose of 5 mg decamethonium (figs. 6A, B) the neuromuscular block showed the signs previously ascribed to a pure depolarization block.

There is some post-tetanic facilitation to be seen in the control (fig. 6A). This phenomenon is only rarely seen in the controls, but to some extent its presence detracts from the value of post-tetanic facilitation alone as a diagnostic measure. It will be noted that it was less in the presence of the depolarization block (fig. 6B).

Repeated additional doses (1.25 mg) led to a gradual lessening of the dose-response relationship, i.e. tachyphylaxis. By the time a dose of 15–20 mg of decamethonium (over a period of 2 hours) had been reached the characteristics of the neuromuscular block showed a marked change. A fade of successive stimuli even with twitch rates of stimulation and post-tetanic facilitation was present (fig. 6C). In other words, the block strongly resembled that seen after a dose of d-tubocurarine.

Recovery of the neuromuscular block at this time was extremely sluggish. The respiratory activity of the patient (if unassisted) was severely depressed, with a marked tracheal tug.

At this point 2.5 mg neostigmine was given intravenously. Three minutes later electromyographic measurement of the hypothenar muscles revealed an almost complete recovery from the neuromuscular block (fig. 6D).

At the same time, respiratory activity improved dramatically to full tidal volume.

Control

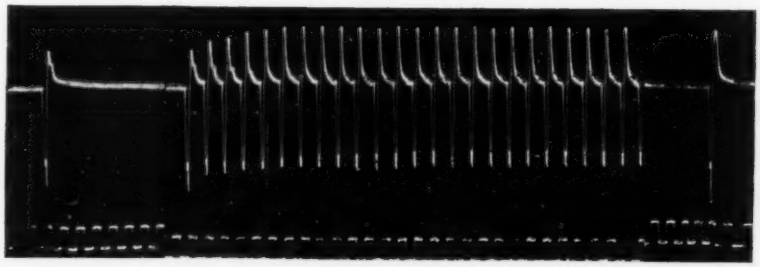

FIG. 6A
Rate of nerve stimulation: 25 per second

After 5 mg decamethonium

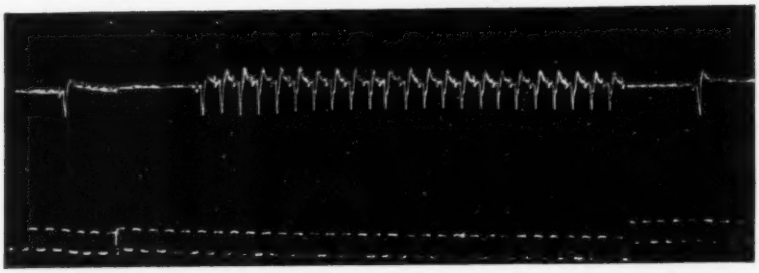

FIG. 6B
Rate of nerve stimulation: 25 per second

After 20 mg decamethonium

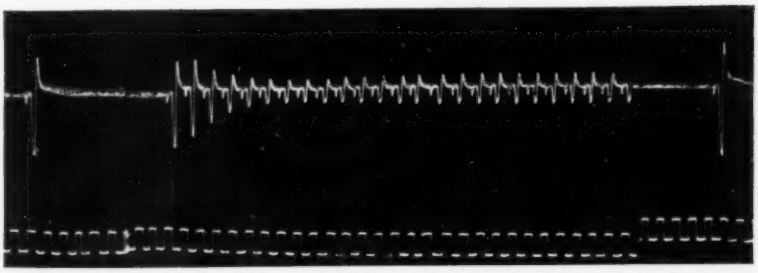

FIG. 6C
Rate of nerve stimulation: 25 per second

2.5 mg neostigmine after 20 mg decamethonium

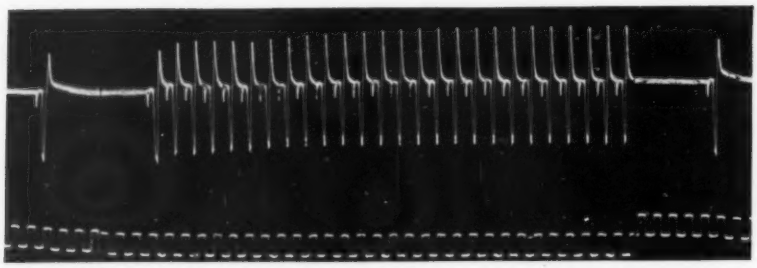

FIG. 6D
Rate of nerve stimulation: 25 per second

DISCUSSION

The foregoing results lead to the following principal findings. First, electromyography reveals a distinct pattern which makes it possible to differentiate between a depolarizing and a non-depolarizing block. Secondly, neostigmine alone, in therapeutic doses, is capable of producing a neuromuscular block. Finally, evidence is presented to show that the type of neuromuscular block produced by both suxamethonium and decamethonium gradually changes as increasing doses are used.

Soon after the introduction of the depolarizing relaxant drugs into clinical anaesthesia reports began to accumulate of an abnormal response. Some patients receiving either decamethonium or suxamethonium showed a prolonged apnoea which promptly responded to neostigmine therapy. Yet it had already been firmly established that anticholinesterase drugs increased the neuromuscular block of a single injection of decamethonium and suxamethonium. It appeared, therefore, that under certain conditions the response of the motor endplate might gradually change from one of depolarization to one of non-depolarization.

The problem of the diagnosis of neuromuscular block was further accentuated by the advent of some new synthetic relaxant drugs. For example, the modes of action of benzoquinonium hydrochloride (Mytolon) (Foldes, 1957) and dioxahexadecaniumbromide (Prestonal) (Frey, 1956; Jolly, 1957) were incompletely understood. More recently, the introduction of a new relaxant drug—hexamethylene 1–6 carbaminoylcholine bromide (Imbretil)—which is claimed to act by both mechanisms, has increased the problem. The results of the application of this electromyographic technique to the latter drug are reported elsewhere (Christie, Wise and Churchill-Davidson, 1959).

Animal studies have revealed that in certain species both decamethonium and suxamethonium are followed first by a neuromuscular block showing the characteristics of depolarization and then by one of the characteristics of nondepolarization Zaimis, 1953). A similar type of block (i.e. dual block) has been described in myasthenic patients (Churchill-Davidson and Richardson, 1953.) Tidal volume studies have suggested that the neuromuscular block produced by the depolarizing drugs gradually underwent a change following successive doses (Brennan, 1956; Foldes et al., 1957; Hamer Hodges, 1958). Nevertheless, such measurements provide no direct proof that neuromuscular transmission is affected. The results reported in this paper, however, demonstrate conclusively that the neuromuscular block following the infusion of both suxamethonium and decamethonium gradually undergoes a change.

The danger of the indiscriminate use of neostigmine is emphasized by the finding that therapeutic doses are capable of producing neuromuscular block. This appears to be achieved by two possible mechanisms. First, by accumulation of acetylcholine molecules with failure of trans-

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mission of rapid rates of stimulation. Secondly, by a direct depolarizing action of neostigmine on the motor endplate. It would seem unwise, therefore, to use this drug after a depolarizing one unless there is absolute proof that the neuromuscular block has undergone a change to the nondepolarizing type. Doses in excess of 2.5–3.75 mg are seldom likely to benefit neuromuscular transmission, even in the presence of severe neuromuscular block.

SUMMARY

A method of diagnosing the type of neuromuscular block in an anaesthetized patient is described.

Evidence is presented to show that the continued infusion of both suxamethonium and decamethonium leads to a change in the type of neuromuscular block.

Therapeutic doses of neostigmine can lead to neuromuscular block.

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THE PHARMACOKINETICS OF HALOTHANE (FLUOTHANE) ANAESTHESIA

BY

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THE absorption and elimination of inhalation anaesthetics were studied at the end of the last century and the beginning of this by Bert (1878, 1883a, b, c), Nicloux (1906a, b, 1907a, b) and other research workers, and their findings were confirmed by Haggard (1924a, b, c, d, e), Robbins (1936), McCollum (1930) and other more recent investigators. The findings of the early workers have been collected in monographs by Winterstein (1926) and Kochmann (1923). They showed that the depth of anaesthesia is dependent upon the concentration of anaesthetic in the blood and central nervous system and that these are controlled by the concentration in the inhaled air. From this it follows that the more rapidly can this concentration in the blood be altered, the easier is the control of the depth of anaesthesia by the anaesthetist.

One of us (Raventós, 1956) studied the concentration of Fluothane (halothane)* in the arterial blood of dogs at different depths of anaesthesia. In these preliminary experiments it was found that when halothane is administered in open circuit its concentration in the arterial blood increases rapidly during induction but can be kept constant during the administration of maintenance concentrations of the agent, and that the concentration falls rapidly soon after the administration of the anaesthetic is stopped. These observations explained the rapid onset of anaesthesia with halothane and the facility with which the anaesthesia could be controlled and reversed.

As several reports on the use of halothane using closed-circuit and to-and-fro techniques have been published since then, it was felt that a closer study of the accumulation and distribution of halothane in the body and its exhalation during recovery was necessary (Marrett, 1957, 1959; Brown and Woods, 1958; Johnstone, 1957). This article describes the results of such a study.

*The word "Fluothane" is a registered trade mark of Imperial Chemical Industries Ltd.

METHODS

Chemical estimation of halothane.

Halothane was estimated in blood, tissues and expired air by the method of Duncan (1959).

Spectrophotometric estimation of halothane.

The concentration of halothane was estimated in several samples of expired air by measurement of the optical density at 204 mμ using a Beckmann D. U. Spectrophotometer. A 1 per cent v/v mixture of halothane in air has an optical density of 0.141 in a 1-cm cell at 204 mμ. The ultraviolet absorption spectrum of halothane has been studied by Kalow (1957).

Preparation of vapour mixtures.

The anaesthetic mixtures used in these experiments were prepared by the method of Raventós (1956).

Accumulation of halothane in mice.

The animals were anaesthetized by our standard methods (Raventós, 1956). Batches of twelve mice were put into the exposure chamber and submitted to the action of halothane for different lengths of time, after which they were removed from the chamber and killed at once by breaking the spinal cord high up in the neck. The carcasses were immediately put into beakers containing petroleum ether, homogenized, and their halothane content estimated as described by Duncan (1959). The weight of the mice was measured by difference. By this method the halothane content of the tissues, including the skin, was measured.

In other experiments the mice were submitted to the action of halothane for a period of 2 hours and allowed to recover in the laboratory from the action of halothane. Groups of these mice were killed at regular intervals and treated by the described method.

Absorption of halothane by the blood and tissues of rats.

The animals were anaesthetized with ether and the trachea and one of the carotid arteries cannulated, after which they were placed on an electrically heated dissection table and the tracheal cannula connected by means of a T-piece to the delivery tube of the apparatus used for the preparation of the anaesthetic mixtures. The other arm of the T-piece was fitted with a nonreturn water valve. The anaesthetic mixtures were produced at a rate of 2 l./min, which is several times greater than the average minute volume of the rat. In this way we ensured that the animals were inhaling the anaesthetic in a constant concentration throughout the experiment without the danger of CO_2 accumulation. The carotid cannula was constructed from a thin capillary tube about 10 cm long which was bent at the middle.

The animals were under the action of halothane for different periods of time, with a maximum of 6 hours. Heparin (0.25 mg) was injected intravenously 5 minutes before bleeding the rats. The blood samples were collected by releasing the bulldog clip which had been placed on the carotid artery and allowing the blood to run into petroleum ether, care being taken to keep the tip of the cannula under the surface of the petroleum ether.

Immediately after taking the blood sample, samples of brain, liver, perirenal fat and other tissues were removed and placed immediately into petroleum ether. All the samples were weighed by difference and analyzed for halothane.

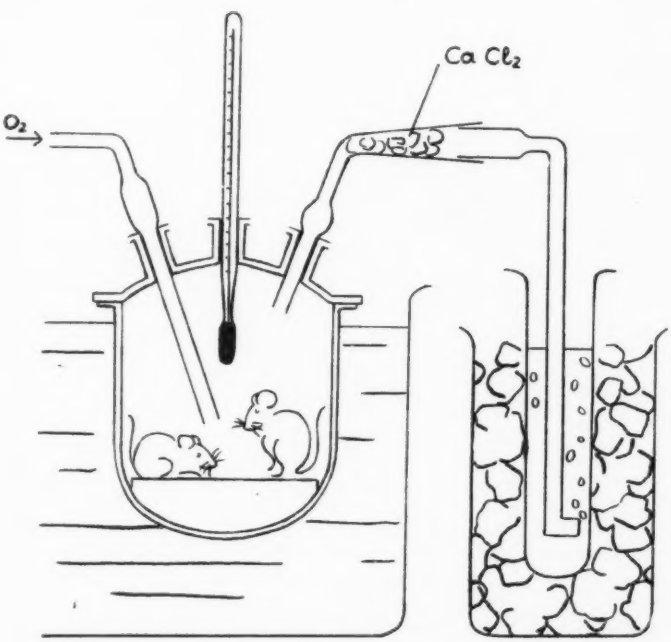

FIG. 1
Apparatus for measuring the amounts of halothane eliminated in the expired air of mice during recovery. (Not to scale).

This procedure was slightly modified in the experiments where the concentration of the anaesthetic was measured during recovery. In these experiments batches of twelve rats were anaesthetized for 2 hours in an exposure chamber larger than the one used in the experiments on mice. At the end of the anaesthesia the rats were taken from the chamber and left to recover in the laboratory. One carotid artery was cannulated while the rat was still under the influence of halothane (or under ether anaesthesia if it had recovered) and at intervals samples of blood and tissues were taken as before.

In some experiments, samples of mixed venous blood were taken into a heparinized syringe by direct puncture of the right ventricle, or by puncture of one of the hepatic veins, the tip of the needle being at the juncture of both cavae. These rats were also anaesthetized with ether if necessary.

Estimation of halothane in the expired air.

Batches of twelve mice were anaesthetized with halothane in the exposure chamber of our apparatus. Six of these mice were killed at the end of the period of anaesthesia and used for the estimation of the total halothane content of their bodies. The other six mice were transferred to recovery chamber of the apparatus shown in figure 1, which was flushed continuously with oxygen at a rate of 100 ml/min. This chamber was a round-bottomed flask (Quickfit FR700F)

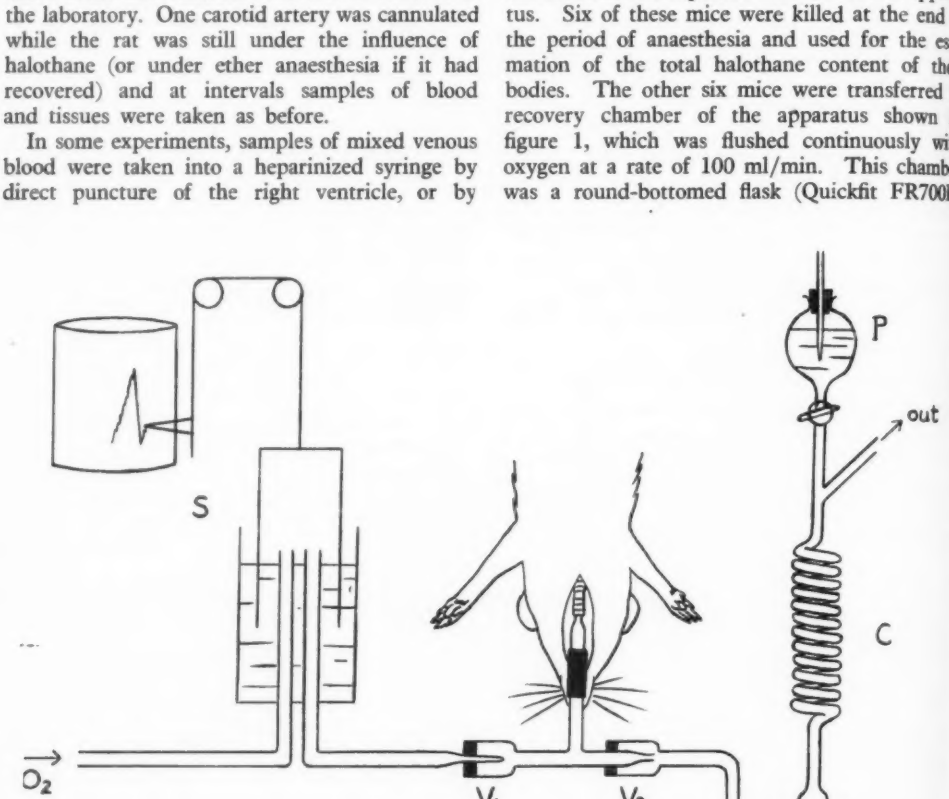

FIG. 2
Apparatus for measuring the elimination of halothane and its concentration in the expired air of rats during recovery. (Not to scale.)

fitted with a multiple adaptor (Quickfit MAF 2/2) and was half submerged in a thermostatically controlled water bath at 25°C. The outlet gases, dried by passing over anhydrous calcium chloride, were bubbled through petroleum ether in test tubes submerged in crushed ice. The petroleum ether tubes were changed every 10 minutes and the halothane in the solvent estimated by the standard method. The mice were kept in the recovery chamber for 2 hours and then killed and their halothane content measured as already described.

In other experiments rats, anaesthetized with allobarbitone (Dial) solution (0.6 mg/kg i.p.), were placed on an electrically warmed operating table and allowed to inhale halothane (1.5 per cent v/v) through a tracheal cannula for 2 hours by the technique described. At the end of this time the tracheal cannula was connected to the apparatus shown in figure 2. The animal inspired oxygen from a spirometer of about 500 ml capacity (S) through a unidirectional valve (V_1) and the expired air passed through the unidirectional valve (V_2) to the side arm of a collection tube (T) and then by a glass coil (C) to the open air.

The halothane in the expired air was extracted by petroleum ether running as a thin layer down the glass coil at a rate of 2 ml/min from a Mariotte bottle reservoir (P). The total amount of oxygen absorbed by the animal from the spirometer was recorded on a smoked drum during the experiment. The collection tube was changed at regular intervals and the halothane content of the petroleum ether samples estimated. In these experiments the total halothane expired by the animal was measured and its concentration in the exhaled air calculated from the spirometer tracings.

The efficiency of the apparatus was tested by passing a stream of 1.5 per cent halothane at 1.1 l./min through the spiral and then passing the air from the outlet tube through petroleum ether. No halothane was found in the latter indicating that extraction by the solvent in the spiral was complete.

In some experiments the expired air of rats during recovery was collected in silica cells and the concentration of halothane estimated spectrophotometrically.

RESULTS

Absorption and elimination of halothane in mice.

The rate of accumulation of halothane in the body of the mouse was estimated by anaesthetizing batches of animals with 1.5 per cent v/v halothane in oxygen and killing the mice after different periods of anaesthesia.

It was found that there was an initial rapid uptake of the agent so that after 10 minutes of inhalation the mice contained approximately 32 mg of halothane/100 g. body weight. Following this rapid uptake the amount of halothane in the body increased more slowly, but progressively, with continued anaesthesia, so that after 3 hours it had reached about 170 mg/100 g.

This concentration of anaesthetic does not represent saturation of the tissues with halothane since, as is shown in figure 3, there was no significant decrease in the rate of uptake of the agent, even after 3 hours of anaesthesia.

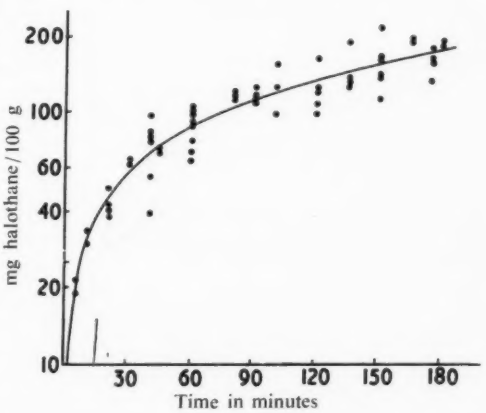

FIG. 3

Absorption of halothane in mice anaesthetized with 1.5 per cent v/v halothane in oxygen. Each point represents one mouse.

The rate of disappearance of the total halothane in mice was studied using animals which had been anaesthetized for 2 hours with 1.7 per cent v/v halothane in oxygen. The animals were then allowed to recover on a warm plate and batches of them killed at intervals. The concentration of halothane in the animals, which was about 200 mg/100 g. at the end of anaesthesia, decreased rapidly

to 150 mg/100 g. in 20 minutes and then to about 15 mg/100 g. in 2 hours. The rate of decrease during recovery was logarithmic, there being a 50 per cent decrease in 30 minutes (fig 4).

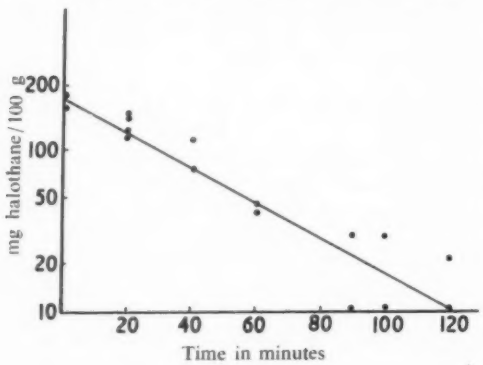

FIG. 4

Decrease in the halothane content of mice during recovery after 2 hours of anaesthesia with 1.7 per cent v/v halothane. Each point represents one mouse.

The distribution of halothane during anaesthesia.

The experiments on mice give an overall picture of the rates of uptake and elimination of halothane from the tissues, without giving any information on its distribution during anaesthesia and recovery. This problem was studied in more detail in experiments on rats where the concentrations of halothane in different tissues were estimated at different times during anaesthesia.

Following inhalation of halothane (1.5 per cent v/v) it was found that the concentration of halothane in the arterial blood increased rapidly and reached an equilibrium with the inhaled vapour mixture in about 1 hour. After this period there was no further increase in the amount of halothane present in the arterial blood; it remained constant at about 20 mg/100 ml for as long as 6 hours anaesthesia.

The concentrations of halothane in the brain and liver were higher than that in the arterial blood and increased steadily during continued anaesthesia. These two organs, which after 30 minutes inhalation of halothane contained about 20 mg of the agent/100 g., accumulated it slowly so that after 6 hours they contained 45–50 mg/100 g.

The accumulation of halothane in the perirenal fat was more rapid than in any other tissue, the concentration of halothane increasing from about

TABLE I

Average concentration of halothane, expressed in mg per 100g, in the tissues of rats anaesthetized for different lengths of time with 1.5 per cent v/v halothane. The figures in parenthesis indicate the number of animals used in the experiments.

Tissue	Duration of anaesthesia (hr.)							
	0.5	1.0	1.5	2.0	2.5	3.0	4.5	6.0
Blood	15.1 (3)	16.9 (3)	18.0 (3)	16.8 (3)	21.0 (3)	22.0 (3)	18.5 (3)	21.5 (3)
Fat	55 (3)	100 (3)	130 (3)	250 (3)	300 (3)	450 (5)	650 (7)	950 (7)
Brain	20 (3)	25 (3)	20 (3)	31 (3)	31 (3)	33 (3)	38 (4)	45 (4)
Liver	17 (3)	22 (3)	18 (3)	23 (3)	26 (3)	35 (3)	43 (4)	48 (4)

55 mg/100 g. after 30 minutes to 950 mg/100 g. after 6 hours anaesthesia. The results (figure 5) show that there was no decrease in the rate of uptake of halothane by the perirenal fat and therefore that a considerably longer period of anaesthesia than 6 hours would be required to saturate the fat at this inhaled concentration of halothane.

The results of these experiments are summarized in table I and figure 5.

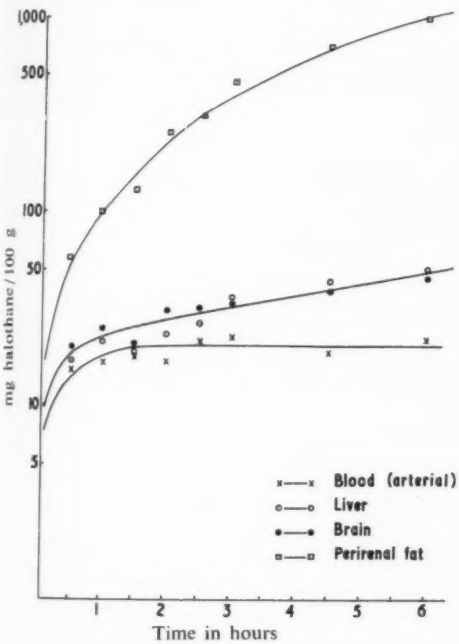

FIG. 5
Mean concentrations of halothane in the tissues of rats anaesthetized with 1.5 per cent v/v halothane.

Elimination of halothane from tissues.

The concentrations of halothane in the arterial and venous blood of rats which had been anaesthetized for 2 hours with 1.5 per cent v/v halothane in oxygen were estimated during recovery. The results (figure 6) show that there is a marked difference in the rate of decrease of the concentration of halothane in the arterial and venous blood after cessation of the inhalation of the agent.

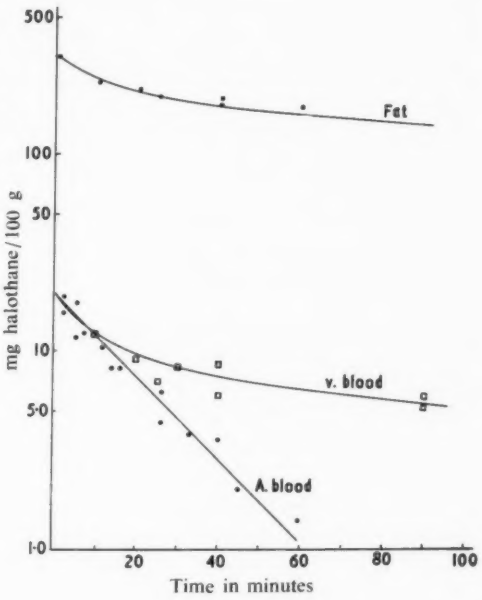

FIG. 6
Concentrations of halothane in the arterial and venous blood and perirenal fat of rats during recovery after 3 hours of anaesthesia with 1.5 per cent v/v halothane. Each point represents one animal.

In the arterial blood the concentration decreased logarithmically from about 20 mg to 1.4 mg/100 ml in 1 hour. This decrease in concentration represents a rate of clearance of approximately 50 per cent in 14 minutes. Twenty minutes after stopping inhalation, at which time the animals displayed voluntary movement, the concentration of halothane in the arterial blood was about 7.5 mg/100 ml.

In the venous blood after an initial rapid fall in the concentration of halothane the decrease was logarithmic. At the end of the first 10 minutes of the recovery period the concentration of halothane was about 12 mg/100 ml venous blood and after 1 hour it was about 6 mg/100 ml. During this part of the recovery period the rate of clearance was 50 per cent in about 45 minutes.

In the same series of experiments the concentration of halothane in the perirenal fat was estimated with results similar to those found for the venous blood. In the first 20 minutes of the re-

covery period the concentration in the perirenal fat decreased from 310 to 230 mg/100 g. At the end of 1 hour the concentration was 180 mg/100 g.; these results represent a 50 per cent clearance from the fat in about 45 minutes, a rate of clearance similar to that found for the venous blood.

Elimination of halothane in the expired air of mice and rats.

Estimations of the halothane present in the expired air were carried out in mice and rats during recovery from anaesthesia, using the techniques described.

In some of these experiments batches of twelve mice were anaesthetized for 2 hours with 1.5 per cent v/v halothane. One half of these animals were sacrificed immediately after the anaesthesia period and their halothane content estimated. The other six mice were placed in the recovery chamber of the apparatus shown in figure 1 which was then flushed for 2 hours with oxygen at a rate of 100 ml/min. The effluent gases from the chamber were passed through petroleum ether which extracted the halothane exhaled by the animals. These mice were killed at the end of the experiment and their halothane content estimated.

The results of these experiments, summarized in table II, show that the exhalation of halothane was rather slow at the beginning of the recovery period but increased 10 to 20 minutes after the mice had been put in the recovery chamber. This abnormal result could be due to the relatively large deadspace of the apparatus and to the intense respiratory depression of the animals at the end of the anaesthesia, which was not corrected until their body temperature increased. About 50–60 per cent of the halothane absorbed by the mice during anaesthesia was exhaled in 2 hours. The mice in this experiment took longer to recover from anaethesia than those in the experiments where the halothane content alone was estimated, and the rate of elimination of halothane was lower.

In rats it was found that the concentration of halothane in the expired air was 10–13 mg per cent (1.2–1.5 per cent v/v) at the start of the recovery period and that the concentration decreased progressively to values of 1–2.5 mg per cent (0.12–0.3 per cent v/v) in 3 hours. The amount of halothane eliminated in the expired air per unit time decreased as the recovery from anaesthesia progressed and the elimination was

TABLE II

Amounts of halothane (mg) in the expired air of batches of 6 mice during recovery from 2 hours of anaesthesia with 1.5 per cent v/v halothane. The results are expressed as accumulative totals.

Experiment	Time after cessation of halothane inhalation (min)						
	10	20	30	50	70	90	120
1	1.4	3.9	8.6	16.3	30.0	44.5	62.0
2	1.4	8.0	15.0	31.0	44.4	52.3	63.0

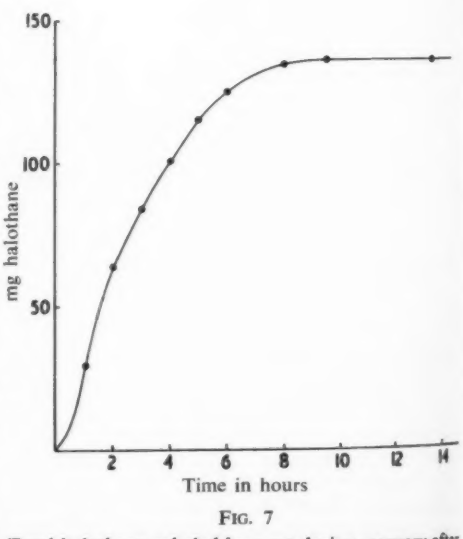

FIG. 7

Total halothane exhaled by a rat during recovery after 2 hours of anaesthesia with 1.5 per cent v/v halothane.

complete in 9 to 10 hours (figure 7), as the expired air collected between 9 and 10 hours, between 12 and 15 hours and between 18 and 21 hours after the end of anaesthesia did not contain any traces of halothane. There was no significant difference between the results of the experiments where the concentration of halothane was measured by the chemical method and those where the spectrophotometric method was used.

The graph (figure 8) shows that at the moment of recovery, as judged by the presence of voluntary movement 20 minutes after the end of anaesthesia, the halothane concentration in the expired air was around 8–10 mg per cent (1 per cent v/v) which is a concentration which can be used for the maintenance of anaesthesia.

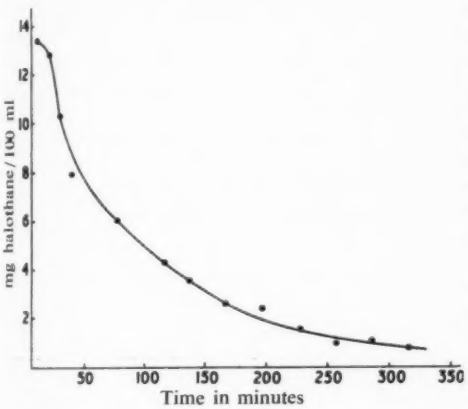

FIG. 8

Concentration of halothane in the expired air of a rat during recovery after 2 hours of anaesthesia with 1.5 per cent v/v halothane.

Metabolism of halothane.

Four different methods have been used to investigate the fate of halothane in the body.

Three rabbits (2–3 kg) were anaesthetized with 1.5 per cent v/v halothane in oxygen for about 3 hours. The animals were bled to death, whilst still under halothane anaesthesia, by placing a cannula in one of the carotid arteries. The blood (40–50 ml) was heparinized and shaken for 10 minutes with cyclohexane (10 ml). The cyclohexane extract was separated by centrifugation and examined by vapour phase chromatography using a column (184 cm × 4 mm) of a 30 per cent chlorinated diphenyl on graded celite at a temperature of 60°C. The carrier gas, dry nitrogen, at a flow rate of 0.9 l./hr. had an inlet pressure of 642 mm Hg with a pressure drop of 361 mm Hg. The effluent gases were examined using a katharometer at 35°C and the galvanometer readings were recorded on a chart moving at a speed of 15.5 cm/hr. The chromatogram of the extracts showed only the characteristic peaks of halothane and cyclohexane.

The second approach to the problem was to examine the urine of animals for trifluoroacetic acid (CF_3COOH) which seemed to be a possible metabolic product of halothane. Two dogs, after anaesthesia for 3 hours with halothane, were placed in a metabolism cage to recover and their urine was collected over the following 24 hours. The urine was acidified, extracted with ether and the ether extract chromatographed on Whatman No. 1 paper using butanol saturated with 2N. ammonium hydroxide as the irrigant. The chromatograms were run for about 16 hours, dried in the open air and then sprayed with a bromophenol indicator solution. No trifluoroacetic acid was detected in the ether extracts by this method which gave good results using synthetic mixtures of urine and trifluoroacetic acid.

The third method involved measurement of the total recovery of halothane from anaesthetized animals. These experiments were combined with those in which exhalation of halothane by mice was measured. The results (table III) show that the total halothane detected in the expired air over a 2-hour period plus the halothane remaining in the mice at the end of this period accounts for 87 and 94 per cent of the halothane found in the control groups of mice killed at the end of the period of anaesthesia.

Finally, a group of six rats was anaesthetized with halothane for two periods of 3 hours in the one day and their urine collected over the following 48 hours. The urine was analyzed for total halide by potentiometric titration and for bromine using the method of Kaplan and Schnerb (1958). No significant differences were observed between the amounts found in the urine from these animals and from untreated rats.

TABLE III

Recovery of halothane in the expired air of mice compared with the amount of halothane in the body at the end of anaesthesia and 2 hours after recovery.

Experiment	Halothane (mg) in mice after 2-hrs. anaesthesia	Halothane (mg) exhaled in 2-hr. recovery period	Halothane (mg) in mice after 2-hr. recovery period	Per cent halothane accounted for
1	120	62	42	87.0
2	87	63	19	94.0

These four experiments, although not conclusive, would seem to indicate that there is little, if any, metabolism of halothane in the body and that it is mainly excreted in the expired air.

Halothane concentrations in the venous blood of patients during anaesthesia and recovery.

Samples of blood from patients undergoing surgical operations of varying complexity and duration were taken from the cubital vein and analyzed for halothane. All the patients were anaesthetized by Dr. M. W. Johnstone with 1.5 to 2.5 per cent v/v halothane in oxygen or in 50 per cent nitrous oxide in open circuit using the trichlorethylene vaporizer of the Boyle's apparatus or with the Fluotec vaporizer. The authors wish to express their gratitude to Dr. Johnstone for allowing them to carry out these estimations.

From thirteen patients, slim to obese and from 25 to 81 years of age, a total of thirty blood samples were taken during the maintenance of anaesthesia. One sample was always taken from each patient no more than 5 minutes before stopping the inhalation of halothane. One or more blood samples were taken from each patient during the recovery from anaesthesia. The data of these estimations are collected in table IV. All

TABLE IV

The concentrations of halothane in the venous blood of patients anaesthetized for varying lengths of time with halothane.

Duration of anaesthesia	Mg halothane per 100 ml venous blood: Time (min) after cessation of inhalation of halothane													Half clearance time (min)
	0	4	6	8	10	12	20	23	25	30	40	45	60	
11 min	5.5			3.2										10
15 „	7.9	4.6												6
16 „	9.9		5.9											8
19 „	17.3		4.7											3
30 „	12.0					4.3					2.0			14
35 „	7.0	6.7								3.4				27
40 „	5.9				3.7						2.5			22
47 „	6.0								3.3			2.1		29
50 „	7.0				5.5					3.0				26
55 „	6.5							4.7						45
60 „	4.9			3.4		2.2	1.5			1.0				10
120 „	6.0		4.4		4.3		3.2						1.4	26
160 „	7.4					4.7					2.5			25

patients, irrespective of the length of anaesthesia, showed vigorous corneal reflexes and responded to commands within 10–15 minutes of the cessation of halothane administration; at this time the concentrations of halothane in the venous blood was 2–4.5 mg/100 ml. The patients can be divided into two groups: those who were anaesthetized for about 30 minutes or less and those who were anaesthetized for more than 30 minutes. In the first group the halothane concentration in the venous blood varied from 5.5 to 17.3 mg/100 ml, with half-clearance times of less than 20 minutes, whilst in the eight patients in the latter group the concentrations varied between 4.9 and 7.4 mg/100 ml and the half-clearance times showed a mean value of about 26 minutes.

Concentration of halothane in the vapour mixture during closed-circuit anaesthesia.

The concentrations of halothane in the rebreathing bag of a Boyle's apparatus was measured during anaesthesia of dogs using a completely closed-circuit technique. Anaesthesia was induced with halothane, without premedication, and the dogs were intubated and put on to a closed circuit for the rest of the experiment. Oxygen was introduced into the circuit at a rate of 200 ml/min and the control of the vaporizer adjusted so that a steady level of anaesthesia was maintained. The concentration of halothane in samples of the gases obtained from the rebreathing bag was measured spectrophotometrically using 5-cm silica gas cells.

In these experiments it was possible to maintain the same depth of anaesthesia, once the control of the vaporizer had been correctly set, for as long as 3 hours, the maximum duration studied. There was no progressive increase in the concentration of halothane in the rebreathing bag, the concentration varying between 2.1 and 2.4 per cent v/v.

DISCUSSION

The results of our experiments offer an explanation of some of the characteristics of the action of halothane. For instance, the short induction period is due to the rapid absorption of halothane by the arterial blood which quickly reaches an equilibrium with the concentration of the inhaled gas, and the rapidity of the transfer across the alveolar membrane is also partly responsible for the short recovery times after anaesthesia. In spite of the large quantities of halothane absorbed by the body during anaesthesia, there is a relatively small amount of agent in the C.N.S. and in the arterial blood, from which it is quickly eliminated after the cessation of the inhalation of the anaesthetic.

The accumulation in the body of inhalation anaesthetics has been studied in the past by determining the amount of agent eliminated in the expired air during recovery. Using this technique Haggard (1924a) deduced that the amount of ether fixed in the tissues at any moment during anaesthesia could be calculated from the concentration in the mixed venous blood. This rule cannot be applied to halothane because the amount absorbed by the body increases progressively during anaesthesia so that calculations based on the concentration in the venous blood give values which are lower than those determined experimentally.

In experiments in which the halothane absorbed by the mouse was measured directly it was observed that the uptake was rapid during the first 20 minutes of anaesthesia, but after this the absorption of the agent continued at a slow but steady rate for the duration of the anaesthesia. In none of the experiments was an equilibrium attained between the concentration of halothane in the inspired air (1.5 per cent v/v) and in the tissues; it is probable that to reach this equilibrium some 20 hours of anaesthesia would be required. This observation is in agreement with those reported for chloroform (Tissot, 1906a) and ether (Haggard, 1924b, c), where the theoretical equilibrium between the inhaled gas mixture and the tissues was not reached.

The uptake of halothane by the different tissues is not uniform as it is influenced by their chemical constitution. The blood, which has a low lipoid content, attains equilibrium with the inspired gas rapidly, whilst the tissues with a higher lipoid content absorb halothane at a constant rate for longer than 6 hours. The high concentrations of halothane in the adipose tissue are not surprising, as halothane has a high oil/water partition coefficient (halothane 330; ether 3.2; chloroform 110). This ratio, which is an indication of how much anaesthetic the fat can absorb when in equilibrium with a known concentration in the blood, does not define the rate of uptake

by the tissues. This is influenced by other factors, such as the blood flow through the organ and the concentrations of the different lipoid fractions present in each tissue. Thus the brain has a higher lipoid concentration than the liver, yet the results obtained for these tissues show that halothane is absorbed at the same rate and in similar concentrations. We presume that this is due to the fact that the brain has a lower blood flow per unit weight than the liver. As these two organs contain less neutral fat than adipose tissue it would appear that halothane is less readily absorbed by phospholipids than by neutral fats.

The perirenal fat absorbs halothane continuously and concentrations between 900 and 1000 mg/100 g were found at the end of 6 hours anaesthesia with 1.5 per cent v/v; this is about fifty times greater than the concentration in the arterial blood. The fat/blood concentration ratio is only 2–3 (Tissot, 1906a, b) for the more water soluble volatile anaesthetics, such as ether and chloroform, and about 1 for barbiturates such as pentobarbitone (Brodie et al., 1953). With the less water soluble barbiturates the fat/blood concentration ratio is greater—12 for thiopentone (Brodie, Bernstein and Mark, 1952) whilst a value of 100 has been reported for n-methyl thiopentone (Peterson et al., 1953). Brodie and his co-workers suggested that the fixation of short acting barbiturates by the fat is the limiting factor of the duration of single i.v. doses of these compounds. This same property also contributes to the quick recovery of animals after hálothane anaesthesia.

During recovery the total halothane in the mouse decreases exponentially with a half-clearance rate of about 30 minutes. When the mice have recovered sufficiently to be able to walk, the brain will contain subanaesthetic concentrations of halothane, although the other tissues still contain relatively large amounts in what must be considered as nonactive depots. The factors which regulate the absorption of halothane during anaesthesia also influence its elimination from the body during recovery. The concentration of halothane in the arterial blood decreases rapidly, with a half-clearance rate of 14 minutes, so that subanaesthetic concentrations are found some 10 to 15 minutes after stopping the inhalation of the agent.

On the other hand, the concentrations of halothane in the venous blood during recovery are always higher than those found in the arterial blood. At the start of the recovery period the concentration decreases at about the same rate as in the arterial blood, but after 10 minutes the rate of clearance falls so that relatively high concentrations are found in the venous blood 2 hours after cessation of inhalation of the agent. Nicloux (1906a, 1907a) and Haggard (1924b) made similar observations with chloroform and ether, but because of the higher blood/gas partition coefficients of these two anaesthetics (halothane 3.6; chloroform 7.3; ether 15) the differences between the concentrations in the venous and arterial bloods were not so great as with halothane.

The rate of clearance of halothane from the few samples of perirenal fat examined during recovery was practically the same as that found in the venous blood (45 minutes). During recovery halothane is released from the fat and other tissues into the venous blood from which the anaesthetic is cleared almost completely during its passage through the lungs. Only small amounts of halothane are carried over into the arterial blood so that no "re-anaesthetization" of the animals can occur.

The elimination of halothane in the expired air during recovery is completed in about 9 hours, which is less than the time necessary for the complete elimination of ether or chloroform. The concentration of halothane in the expired air immediately after anaesthesia is approximately the same as the concentration used during the anaesthesia and it decreases during recovery. Concentrations of 1 per cent v/v, which will maintain anaesthesia in rats, were found in the exhaled air of animals previously anaesthetized with 1.5 per cent v/v when they had recovered sufficiently to be able to walk.

Significant differences in the rate of elimination of halothane during recovery were found in experiments on mice. If the mice were left to recover on a warm plate in the laboratory, the half-clearance rate was about 30 minutes, whilst in other experiments only 52 per cent and 72 per cent (table III) of the total halothane originally present in the body were exhaled in 2 hours. This anomaly is apparently due to the fact that mice show an intense respiratory depression and hypo-

thermia after an anaesthesia of 2 or 3 hours. These effects are longer-lasting if the animals are left to recover in the chamber of our apparatus (figure 1), which is flushed continuously with a stream of oxygen, so that the recovery times of these mice were considerably longer than those used in the other experiments. These results show that, as in the case of ether (Haggard, 1924e), the elimination of halothane is influenced by changes in the respiratory minute volume of the animals.

The concentrations of halothane found in the venous blood of human patients (table IV) were lower than those found in experimental animals; a similar observation was made by Morris, Frederickson and Orth (1951) for chloroform. It is difficult to discuss the significance of these results because the concentration found in the venous blood depends on the depth and duration of anaesthesia and on the site of sampling. In spite of these limitations it was observed that the half-clearance times of halothane from the venous blood of patients who had been anaesthetized for 35 minutes or longer were fairly consistent, varying from 10 to 45 minutes with a mean of 26 minutes; this value is very similar to that found in mice and rats after long anaesthesias. In anaesthesias shorter than 30 minutes the half-clearance times were more irregular but were all less than those observed for the longer anaesthesias.

During the first 30 to 60 minutes of anaesthesia halothane is being distributed throughout the body fluids and only a small fraction of the quantity inhaled is being absorbed by the tissue fats. Therefore the half-clearance time of halothane from the venous blood is proportional to the amount distributed throughout the body, being shorter in brief anaesthesias and greater in longer anaesthesias, since the anaesthetic has been accumulated in certain tissue depots, from which it is cleared during recovery.

Butler (1958) derived a formula from which the half-clearance time of an anaesthetic from the whole body can be calculated approximately.

$$\text{Half life in minutes} = \ln.2 \times \frac{Vd(Vp + \lambda Cp)}{Vp \times Cp}$$

where Vd = apparent volume of distribution of the drug in litres.

Vp = effective pulmonary ventilation in l./min.

Cp = pulmonary circulation in l./min.

λ = the blood/air distribution coefficient of the anaesthetic.

ln.2 = natural logarithm 2.

For comparison we can assume that for man the Vd for halothane, chloroform and ether is approximately the same, and is 70 l.; Vp is 8 l./min; Cp is 5 l./min and λ halothane is 3.6; λ chloroform is 7.3 and λ ether is 15. Therefore, using these values, the calculated half-clearance time of halothane is 31 minutes, chloroform is 54 minutes, and ether is 100 minutes.

It is interesting to note that the half-clearance time of halothane from the whole mouse was approximately 30 minutes; from the perirenal fat and venous blood of the rat around 45 minutes and from the venous blood of man around 26 minutes, values that are in close agreement with that calculated from the above formula. This relatively small clearance time for halothane is the reason for the shorter recovery time after halothane anaesthesia compared to that found after ether and chloroform anaesthesias.

The importance of the uptake of halothane by the tissues is more evident during closed-circuit anaesthesia. Marrett (1957, 1959) and Brown and Woods (1958) using the closed-circuit circle and Johnstone (1957) with the to-and-fro methods of anaesthesia have reported that during anaesthesia there is no build-up in the concentration of halothane in the circuit. This has been confirmed by experiments on dogs anaesthetized in closed circuit with halothane for over 3 hours, where it was found that the concentration of agent in the rebreathing bag remained constant within the limits of 2.1 and 2.4 per cent v/v without any alteration in the setting of the vaporizer. The vaporizer, at the setting used in these experiments, delivered around 0.2 per cent v/v at a flow rate approximately the same as the minute volume of the dogs. Therefore these animals, of an average weight of 12 kg, absorbed 15 to 20 mg of halothane per minute, which is equivalent to 90 to 120 mg for a 70-kg man. This last figure is in agreement with the results of Robson et al. (1958) who found that their patients absorbed 3 to 5 ml of halothane per hour, equivalent to 95–155 mg/min. If the vaporizer of an

anaesthesia apparatus delivers halothane more rapidly than the subject can absorb it there will be an increase in the concentration in the circuit. However, experience has shown that during closed-circuit anaesthesia it is possible to maintain this equilibrium between the amount absorbed by the body and the halothane volatilized in the circuit. If the vaporizer is included in the circuit, the rate of volatilization of the agent depends to a great extent on the respiratory minute volume of the subject and, if this changes because of variations in the depth of anaesthesia, the rate of volatilization of the agent will vary accordingly. Therefore, with spontaneous respiration, these changes will tend to keep constant the concentration of halothane in the circuit and to achieve a steady level of anaesthesia.

Predictions are usually made about the possible metabolism of any new drug and it was considered possible that halothane could be metabolized. However, four different analytical procedures have given negative results, so that we feel justified in stating that halothane is not metabolized but is eliminated unchanged in the expired air during recovery.

SUMMARY

The absorption, distribution and elimination of halothane has been studied using rats and mice. The results of these experiments show that:

(1) The anaesthetic is rapidly absorbed during induction.

(2) The concentration of halothane in the arterial blood reaches an equilibrium with the inhaled concentration in a relatively short time, after which it remains constant.

(3) The concentration of halothane in the brain and liver increases slowly during anaesthesia, whereas there is a more rapid accumulation of the anaesthetic by the adipose tissue. It is estimated that some 20 to 30 hours of anaesthesia with 1.5 per cent v/v halothane would be required to saturate the adipose tissue with the agent.

(4) As the brain does not absorb large amounts of halothane and because of the low blood/gas partition coefficient of this anaesthetic, the recovery from anaesthesia is more rapid than with ether or chloroform.

(5) The halothane fixed in the body during anaesthesias of 3 hours duration is completely eliminated in 9 to 10 hours.

(6) Because of the fixation of halothane by the tissues there is no build–up in the concentration of halothane in the circuit during closed-circuit anaesthesia.

(7) Attempts to demonstrate metabolic products of halothane were unsuccessful and it is assumed that it is not metabolized.

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THE ESTIMATION OF HALOTHANE IN TISSUES

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IN an appendix to a paper by Raventós (1956) on the pharmacology of halothane, Goodall described a method for the estimation of the drug in blood. Halothane was extracted from the blood with petroleum ether and then hydrolyzed under pressure by sodium amoxide. The yield of halide was low, only 60–80 per cent of the bromine being liberated, and although reproducible results could be obtained the method required very careful manipulation by the operator. Efforts were made to improve this method by finding a reaction which increased the amount of halide liberated and which could be carried out at room temperature and atmospheric pressure. The method described is the result of these efforts. It depends on the extraction of halothane from blood or tissues into petroleum ether and the addition of a reducing agent (lithium aluminium hydride) to the extract to liberate the halides. They are then converted to salts by the addition of silver nitrate and these in turn are estimated photometrically.

REAGENTS

(1) *Anhydrous diethyl ether.* The traces of water present in commercially available sodium-dried diethyl ether were removed by the addition of sodium wire.

(2) *Special reagent.* Lithium aluminium hydride (500 mg) was refluxed with the diethyl ether (20 ml) for 4 hours, cooled and then filtered through a No. 3 sintered glass funnel. The residue was washed with a little ether and the combined filtrates diluted to 100 ml with the diethyl ether in a standard flask. The reagent is stable for several days if stored under nitrogen; contact with moist air results in a gradual loss of activity due to the formation of lithium and aluminium hydroxides. As lithium aluminium hydride reacts violently with water care must be taken in handling the reagent. The insoluble residue should be destroyed by the careful addition of 50 per cent sulphuric acid.

(3) *Petroleum ether.* Petroleum ether b.p. 60–80°C and b.p. 100–120°C were used to extract the halothane from tissues and blood respectively.

(4) *Sulphuric acid.* Equal volumes of water and concentrated sulphuric acid (A.R.) were mixed.

(5) *Silver nitrate solution.* 0.01 N silver nitrate was prepared as required by dilution of 0.1 N solution.

(6) *Standard solutions of halothane.* Halothane (120–130 mg) was weighed accurately by difference in a weighing bottle containing 10–12 ml petroleum ether (b.p. 100–120°C). The solution was then transferred to a 250-ml standard flask and diluted with petroleum ether to the mark. A series of standard solutions, containing 0.05–0.30 mg halothane/ml, were prepared from this solution and samples treated as described below.

PROCEDURE

Extraction of halothane from blood.

Samples of blood (4ml), withdrawn from heparinized animals by syringe were added to tubes with ground glass stoppers containing 5 ml petroleum ether (b.p. 100–120°C) by placing the tip of the needle under the surface of the solvent, thereby eliminating any loss of the anaesthetic from the blood to air. If the blood contained no anticoagulant a solution of potassium oxalate (0.25 ml, 5 per cent) was added to each tube before addition of the blood. The halothane was extracted from the blood by shaking the stoppered tubes for 1–2 minutes, the

solvent separated by centrifugation and aliquots (4 ml) of the petroleum ether extracts transferred to numbered test tubes (6 inches × ½ inch) for the reaction.

Extraction of halothane from tissues.

The tissue samples, the weight of which was determined by difference, were added to beakers or test tubes containing petroleum ether (b.p. 60–80°C) immediately after removal from the animal. The tissues were homogenized, using an Atomix with the rubber seal of the container replaced by a polythene one, and the homogenates were diluted to a suitable volume with the solvent and the cell debris removed by centrifugation. Aliquots (10 ml) of the supernatant fluid were distilled using a water bath at 80–90°C until about 8.5 ml of distillate were collected. Samples (4 ml) of the distillates were transferred to numbered test tubes for the reaction.

Extraction from gas mixtures.

Halothane was extracted from gas samples by bubbling the gas through petroleum ether (b.p. 100–120°C) and then diluting the solution to a known volume with the solvent. Samples of the extracts were transferred to numbered test tubes for the reaction.

Reaction.

To each tube containing 4 ml halothane standard solutions or extracts was added 1 ml lithium aluminium hydride reagent. After mixing by shaking, the tubes were allowed to stand at room temperature for 20 minutes. The excess reagent was destroyed by the addition of 1 ml 50 per cent sulphuric acid followed by 5 ml distilled water.

Determination of the halide.

The halide, released by the reduction of halothane, was extracted into the lower aqueous phase by gentle agitation with a glass rod. After allowing the aqueous and organic layers to separate, samples (5 ml) of the aqueous layers were transferred to clean test tubes. Silver nitrate (2 ml) was added, the tubes shaken to ensure mixing and then placed immediately in a dark cupboard. After exactly 10 minutes the optical density of each colloidal suspension of silver halide was measured in a 1-cm cell at 520 mμ against water, using a Unicam S.P. 600 spectrophotometer or similar instrument. The reading for the blank determination (0.06–0.08) was subtracted from the density readings of each of the standards and the corrected optical densities of the standards plotted against their known concentrations. In the same way the optical densities found for the blood and tissue samples were corrected by subtracting the values found for the blood or tissue blank obtained from animals which had not been exposed to halothane. The concentration of halothane in each sample was then calculated from the calibration curve. Because of an enrichment of halothane during the distillation of the tissue extracts the observed values must be corrected by a factor of 0.85.

Recovery from blood and tissues.

Halothane (about 20 mg) was weighed accurately into a small thin glass ampoule which was then placed in a 100-ml flask containing oxalated blood (25 ml) and several glass beads. The flask was sealed with a stoppered reservoir which had a thin concave glass seal at its lower end and the joints were made gas tight with silicone grease. The flask was shaken to break the ampoule and then for several minutes to ensure complete solution of the halothane in the blood; a piece of glass rod, of such a diameter that it would not pass through the bottom of the reservoir after breaking the seal, and petroleum ether (25 ml, b.p. 100–120°C) were added to the reservoir which was then stoppered. A few sharp vertical movements of the apparatus broke the glass seal and allowed the petroleum ether to flow into the flask without loss of air. The apparatus was thoroughly rinsed with the blood-petroleum ether mixture before removal of the stopper; the petroleum ether was separated by centrifugation and its halothane content estimated.

Tissue samples from animals which had not been exposed to the action of halothane were homogenized with petroleum ether (b.p. 60–80°C) containing known concentrations of halothane. The halothane in the petroleum ether "extracts" was then estimated as described above for the tissues of anaesthetized animals.

Action of lithium aluminium hydride on halothane.

Aliquots (1 ml) of the reagent, prepared as above, were added to samples (4 ml) of standard solutions of halothane in petroleum ether and after 20 minutes the excess reagent was destroyed by the addition of water (5 ml), omitting the addition of acid which interferes with the bromide estimation. The halide was extracted into the lower aqueous phase which was separated and filtered.

To samples (2 ml) of the filtrate was added acetic acid (2 ml, 50 per cent) and the total liberated halide, i.e. bromide + chloride, estimated by potentiometric titration with 0.01 N silver nitrate.

Sodium chloride (1 ml, 10 per cent), sodium dihydrogen phosphate dihydrate (2 ml, 15 per cent) and sodium hypochlorite (1 ml, 10–14 per cent w/w chlorine) were added to a sample (2 ml) of the filtrate which was then heated and maintained at the boiling point for 1 minute. The solution was cooled and the excess reagent destroyed by the addition of sodium formate (1 ml, 2 per cent) and heating at 100°C for 5 minutes. To the cooled solution was added water (5 ml), potassium iodide (2 ml, 2 per cent), 1 drop of ammonium molybdate (10 per cent) and sulphuric acid (2 ml, 6N). The iodine was titrated with 0.01 N sodium thiosulphate using starch indicator.

1 ml of 0.01 N thiosulphate = 0.1332 mg bromine.

RESULTS AND DISCUSSION

Lithium aluminium hydride, a powerful reducing agent, is widely used in preparative organic chemistry (Gaylord, 1956) and has been used to remove halide from halogen-containing compounds. The reagent, commercially available, contains halide impurities which must be removed if it is to be used as an analytical reagent and various methods of purification were tried before selecting the described method which was considered to be the most convenient for routine use. The reagent prepared in this way contains 0.27–0.3 per cent lithium aluminium hydride w/v and when used in blank determinations will give optical density readings of 0.08 or less.

The halide released from the halothane has been determined as bromide by oxidation to bromate and as chloride by difference from the total halide which was estimated by potentiometric titration with silver nitrate. The results (fig. 1) show that the release of the bromine is

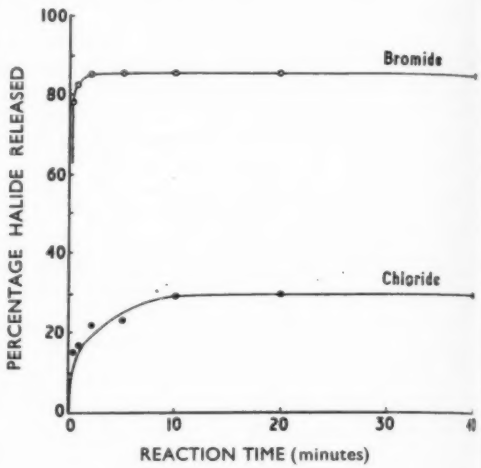

FIG. 1

Time reaction curves of the release of halide from halothane on reduction with $LiAlH_4$

rapid, the reaction being complete within 3 minutes in an 85 per cent yield, whilst only 30 per cent of the chloride is released, this reaction being completed within 10–12 minutes. The reduction is evidently complex but the results are reproducible. For routine use the halide is estimated more conveniently as colloidal silver halide and the halothane content estimated by comparison with known concentrations of halothane in petroleum ether.

Goodall recommended the use of standard solutions of halothane in blood where knowledge of the absolute concentration in blood samples was required (Raventós, 1956). Robson and Welt (1957), who have used this method, also reported that the extraction of halothane from blood with petroleum ether was about 73 per cent. However, I have found that using the methods described at least 97 per cent of the halothane in the blood is extracted with the petroleum ether (fig. 2). Quantitative estimation may therefore be carried out using a calibration curve based on a standard solution of halothane in petroleum ether. No

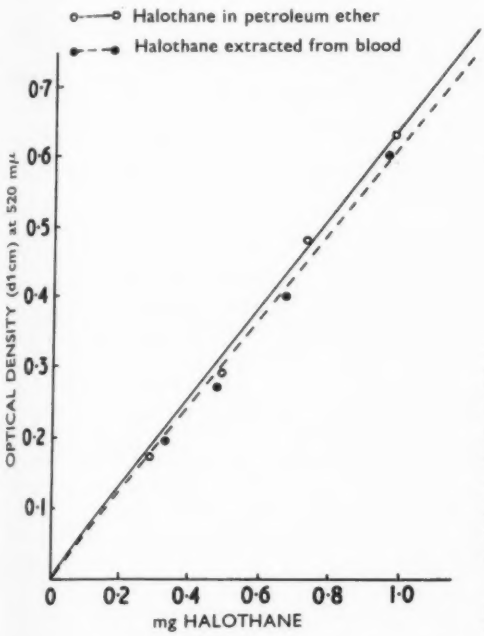

FIG. 2
The recovery of halothane from blood on extraction with petroleum ether.

significant amount of free halide is extracted from blood by petroleum ether but interfering substances are extracted from tissues. The petroleum ether extracts of tissues must therefore be distilled and the same volume of distillate always collected as the halothane distils over in the first 5 ml of the petroleum ether. This is due to the higher boiling point of the petroleum ether used; however, it would be a disadvantage to use a lower boiling point petroleum ether fraction because of the difficulties which would arise in homogenizing the tissues and in general handling. If, as recommended, 8.5 ml of distillate is collected the amount present in the tissue equals the amount found corrected by a factor of 0.85 (table I) which must be allowed for in the final calculations.

The most important precautions to be observed in the method are the use of completely anhydrous diethyl ether for the preparation of the reagent and the complete separation of the aqueous halide extract from the organic phase in the last stage.

TABLE I
Recovery of halothane from fat samples on homogenization with petroleum ether (b.p. 60–80°C)

Halothane added μg	Halothane found μg	Halothane found × 0.85
5,000	6,400	5,400
5,000	5,970	5,050
5,000	5,600	4,760
5,000	6,000	5,100
2,000	2,500	2,130
2,000	2,300	1,960
1,000	1,300	1,100
1,000	1,220	1,040
500	590	500
500	530	450

If this is not observed the blank determinations will give high optical density readings and the results will be erratic. Except for the withdrawal of the blood samples all measurements were carried out using glass pipettes which are more accurate and less vulnerable to chemical attack than syringes and stainless steel needles which were used by Robson and Welt (1957).

Analysis of duplicate samples of halothane in petroleum ether showed that the method has a standard deviation of ±7 per cent over the range of concentrations used (table II). A standard error

TABLE II
Assessment of accuracy of method

Halothane added μg	Optical density	Optical density per 100 μg Halothane
421	0.217	0.518
421	0.251	0.595
421	0.211	0.500
421	0.242	0.571
421	0.221	0.521
421	0.263	0.621
421	0.228	0.541
842	0.511	0.608
842	0.507	0.601
842	0.478	0.569
842	0.504	0.600
842	0.501	0.600
842	0.468	0.558
842	0.468	0.558
1263	0.803	0.638
1263	0.803	0.638
1263	0.823	0.645
1263	0.813	0.639
1263	0.793	0.631
1263	0.803	0.638

Mean optical density per 100 μg halothane = 0.589
Standard deviation = ±0.044

of ±1.14 mg over the range 11–18 mg halothane per 100 ml was reported by Robson and Welt. The measurement of the reagent is the greatest contributing factor to this deviation but the method is, however, sufficiently accurate for normal purposes.

SUMMARY

A method is described for the estimation of halothane in blood and tissues. Halothane is extracted from blood (recovery 97 per cent) and tissues with petroleum ether and reduced with lithium aluminium hydride at room temperature; 85 per cent of the bromine and 30 per cent of the chlorine are liberated and the combined halides estimated nephelometrically as the silver salts.

The method is sufficiently accurate for routine use with a standard deviation of 7.6 per cent.

ACKNOWLEDGMENT

The author wishes to express his gratitude to Mr. G. Macdonald for technical assistance.

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BOOK REVIEW

Instrumentation in Anesthesiology. By W. H. L. Dornette and V. L. Brechner. Published by Kimpton, London. Pp. 242; illustrated. Price 60*s*.

Many anaesthetists deny the utility of measuring instruments in clinical anaesthesia, preferring to rely on clinical signs, and this attitude is supported by the manufacturers of anaesthetic equipment, who forty years after the introduction of the gas machine into this country still supply standard equipment which still gives no adequate indication of the concentration of volatile anaesthetics delivered to the patient. Yet no person who has had a scientific training can deny the value of measurement as a corrective to clinical judgment.

This work may be considered a very useful supplement to Professor Mackintosh's *Physics for the Anaesthetist* which does not consider electronic equipment now in common use in the operating theatre. Sufficient information is given to enable those with an elementary knowledge of physics to understand the basic principles of operation of the commercial apparatus described which is, incidentally, almost entirely of United States manufacture. More attention should have been paid to the critical examination of instrument error in the equipment. The section on flow-rate meters for gases is inadequate and no information is given on calibrated vaporizers for volatile anaesthetics. The only cardiac monitor described operates on a signal from the electrical activity of the heart muscle and gives no advance information of circulatory failure other than that associated with gross cardiac arrhythmias.

The publication is a useful handbook for those engaged in clinical research or the anaesthetist engaged in brain or heart surgery.

Victor Keating

CORRECTION

In a recent review it was stated that the M.R.C. Committee on Non-explosive Anaesthetics had abandoned the view that the hypotension present during halothane anaesthesia was due to cardiac depression. In their report on halothane the Committee said "The evidence suggests that the hypotension is due to a depression of central vasomotor centres combined with diminished cardiac output."

Professor J. H. Burn, who is Chairman of the Committee has written to say that so far as he is aware the Committee has not changed its view.

Brit. J. Anaesth. (1959), **31**, 321.

A MARRETT DRAW-OVER INHALER MODIFIED FOR HALOTHANE

BY

M. A. WOODS AND T. A. BROWN

North Down Group of Hospitals, Northern Ireland

THE satisfaction given by halothane as the principal anaesthetic agent in the general surgical practice of this hospital group (Brown and Woods, 1958a), caused us to explore its suitability for use in the obstetric unit.

We had already substituted closed circuit halothane for cyclopropane, without ill effects, in anaesthesia for Caesarean section. Accordingly, nitrous oxide-oxygen-halothane in a semiclosed circuit replaced cyclopropane and the nitrous oxide-oxygen-trichloroethylene-ether sequence for such procedures as artificial rupture of the membranes, forceps delivery, and breech extraction. No intravenous barbiturate has been used.

The quick and easy induction, the early muscular relaxation and the absence of foetal narcosis impressed our obstetric colleague. He asked us to devise for him a simple, safe, easily portable halothane apparatus with which general practitioners could anaesthetize those of his patients requiring domiciliary operative delivery.

This briefing obviously precluded any method involving the use of compressed gases. The only alternative was to use air as the vaporizing agent and vehicle for halothane.

THE APPARATUS

The open mask/drop bottle method mentioned by Bryce-Smith (Bryce-Smith and O'Brien, 1956) was discarded as wasteful and potentially dangerous in the hands of an occasional anaesthetist. A draw-over vaporizer seemed indicated, and it was decided to use as a basis the trichloroethylene vaporizer of a Marrett draw-over trichloroethylene-ether-air machine, Marrett, 1942). This soundly designed piece of apparatus has a removable one-way inspiratory valve, offers practically no resistance to respiration, and its control lever enables any desired fraction of the inspired air to be passed through the bottle.

After some experiment we found that only one alteration was necessary for its use with halothane. The wick was removed and replaced by a light copper sleeve fitted tightly round the semicircular wick mount (figs. 1, 2, 3). This sleeve serves the dual purpose of occluding the perforations in the wick mount and lengthening it by 1¼ inches (3 cm.), thus ensuring that even small amounts of

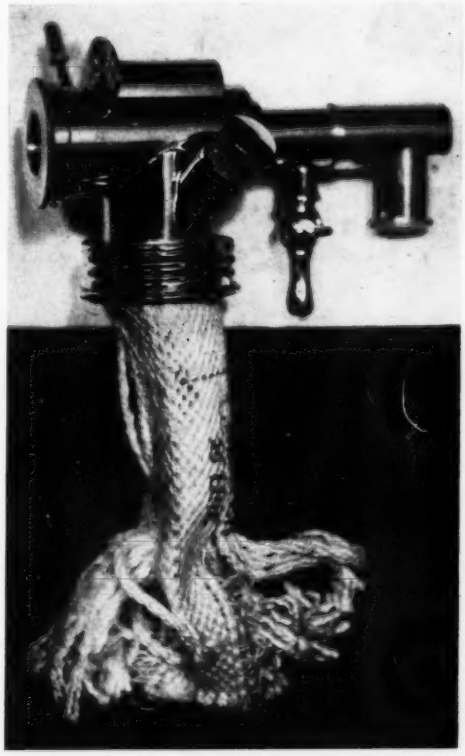

FIG. 1

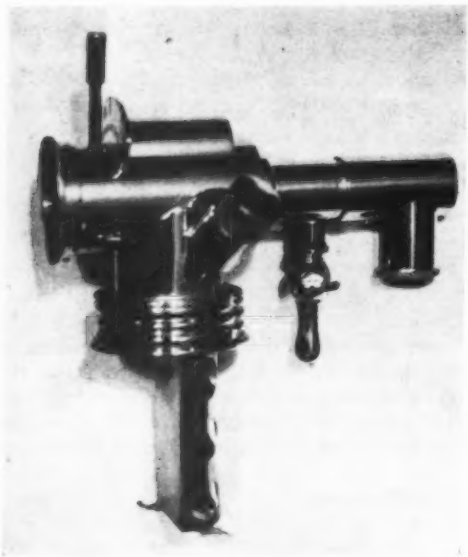

FIG. 2

FIG. 3

air directed down the sleeve by the baffles in the vaporizer head will vaporize some halothane before emerging from the outlet port to mix with the main stream of inhaled air.

A glance at the diagram relating port opening to control lever setting shows that at setting 1 (Fig. 4a) with the lever vertical the vaporizer ports are slightly open. This is the minimum effective setting. At setting 5 (fig. 4c) the control is full on and all the patient's inspired air is passing through the bottle.

It is convenient to file three equidistant notches in the metal scale between these two points, giving five numbered positions for the control lever.

A recessed wooden base into which the bottle fits snugly should be provided to lessen the risk of overturning.

TECHNIQUE

Atropine 0.65 mg (1/100 grain) is given intravenously. 100 ml of halothane are put into the bottle, the inspiratory valve fitted, the hose mount plugged in, and the mask applied to the patient's face. With the expiratory valve fully open, the control lever is turned to the first mark. After a few breaths the control should be gradually advanced to the second mark, and thereafter as fast as the patient's reactions will allow until the fifth mark is reached. This will probably take about 3 minutes.

When the pupils are fixed, central and contracted, the arm muscles flaccid, and automatic respiration well established, the operator may commence and the halothane concentration can be reduced for maintenance. Light third stage anaesthesia can usually be maintained with the control set somewhere between the first and second marks, but the concentration required varies with individuals.

In operative midwifery we make it a principle to keep anaesthesia as light as surgical requirements permit, removing the mask when delivery is imminent. The consequent rapid fall in the blood levels of halothane in both mother and child obviates foetal narcosis. After ligation of the cord, anaesthesia can be rapidly deepened while any necessary suturing takes place, and stopped when the last stitch has been inserted.

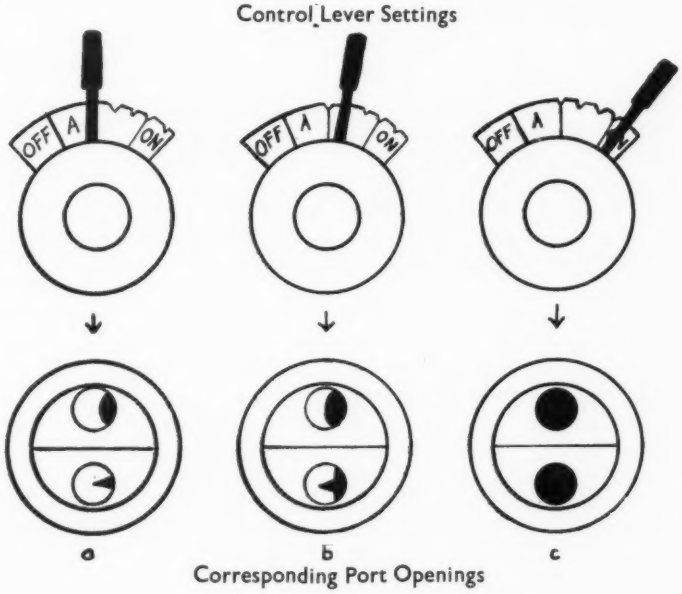

FIG. 4

RESULTS

We find that cases conducted in this way show no increased tendency towards either delayed separation of the placenta or postpartum haemorrhage.

The apparatus has been constantly in use in the casualty room to provide anaesthesia for the reduction of minor fractures and dislocations and the toilet and suturing of wounds. House surgeons are much more interested in learning to use the draw-over inhaler than any method involving conventional anaesthetic machines.

The similarity in principle between the modified bottle and the intrinsic vaporizer of most circle units led us to examine its performance under closed circuit conditions. Removal of the inspiratory valve enabled the bottle to be interposed between the unit and inspiratory hose of a Coxeter-Mushin absorber. With 50 ml of halothane in both the bottle and Coxeter-Mushin ether vaporizer it was then possible to compare performance by switching from one vaporizer to the other during anaesthesia.

Judged clinically the range of halothane vapour concentrations delivered by the bottle between notches 1 and 5 is similar to that given by the Coxeter-Mushin vaporizer between the marks "¼" and "Full on". Surgical anaesthesia can usually be maintained with the bottle control between notches 1 and 2. A detailed description of a suitable closed circuit induction technique has already been described by the writers (Brown and Woods, 1958a).

A Boyle II circle unit which had been discarded for closed circuit work because of metallurgical incompatibility between its intrinsic vaporizer and halothane has given no trouble during several months of daily use with the bottle plugged in as described above. The same procedure can be adopted with Coxeter-Mushin marks 1 and 2 machines, avoiding any necessity for the modifications described in our earlier paper (Brown and Woods, 1958b).

A laboratory test using a mechanical pump with a stroke volume of 500 ml and a minute volume of 10 litres showed that when charged with 100 ml of halothane the bottle delivered at room temperature halothane vapour in air in concentrations ranging from 0.3 per cent v/v at mark 1 to 3.1 per cent v/v at mark 5. Concentra-

tions were determined by means of a gas interference refractometer.

ACKNOWLEDGMENTS

We are indebted to Mr. John Beale of I.C.I. for his encouragement and liberal supplies of halothane and to Mr. John Cockton, Ph.C., of I.C.I., who kindly undertook the estimations of halothane vapour concentration. The photographic illustrations are the work of Mr. John Macgouran, M.S.R., our Superintendent Radiographer.

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BOOK REVIEW

Fundamentals of General Anaesthesia for Students and Practitioners of Dentistry. By John Adriani, M.D. Published by Charles C. Thomas, Springfield Illinois, U.S.A. and Blackwell Scientific Publications, Oxford. Pp., 213; illustrated. Price 50*s*.

This is another "Adriani", but in this book a well-respected author will not be found entirely authoritative—for the British reader at any rate. To quote from the preface: "Emphasis is placed on the physiology, pharmacology, indications, type of drugs, preparations, hazards and the complications of general surgery which apply to dentistry and oral surgery." This is all very well but the British anaesthetist who wishes to learn more about dental anaesthesia is likely to be cognizant of all these aspects of general anaesthesia. The dental surgeon, on the other hand, to whom this book might appeal, will require mainly instruction in technique and in this respect the author has been found wanting. The whole book comprises 213 pages, yet the section dealing with "technique of administration" for what are termed "office procedures" consists of 11 pages only. In this section we find the following advice: "The patient is placed in the dental chair, his legs and wrists are restrained and collar is loosened, the psychological approach to the patient is important particularly if no premedication is used . . . . Anaesthesia is first induced with a face mask which covers both the mouth and the nose. As soon as stage three is attained the mask is replaced by a nasal attachment."

Few British anaesthetists restrain their patients before anaesthesia has been induced and it is many years since the reviewer has heard of anyone commencing the induction of anaesthesia in adults with a facepiece and afterwards changing to a "nasal attachment". Although it is stated that a pack is used and an illustration provided showing one in position, no mention is made of the most suitable type of material to use for this purpose, nor is it indicated that part of the pack or a firmly attached tape must always be readily available outside the mouth as a safeguard, in case it is necessary to pull it forwards when an obstruction is suspected.

These few examples will suffice to show that, whereas this work may be valuable for reference for the basic principles of anaesthesia, as a practical guide it is a disappointment. This is a pity as a great deal of trouble has been taken over its preparation, the type is easy to read, it is printed on art paper and well bound.

Victor Goldman

Brit. J. Anaesth. (1959), **31**, 325

THE LUBRICATION OF ENDOTRACHEAL TUBES WITH POLYETHYLENE GLYCOLS

BY

RUSSELL M. DAVIES AND F. H. SUMMERS

The Queen Victoria Hospital, East Grinstead, England

ANAESTHETIC tubes used for endotracheal and intranasal insertion are usually lubricated with soft paraffin or with water-based gels. We have found that the latter do not adhere well to the tube, while soft paraffin has several disadvantages; its nonmiscibility with water makes the cleaning of tubes so lubricated difficult and it produces rapid deterioration of the rubber of which most tubes are made. Repeated use of paraffin might, if absorbed, cause a paraffinoma (*Brit. Nat. Form.*, 1957a), and the inhalation of liquid paraffin has been reported to cause lipoid pneumonia (*Brit. Nat. Form.*, 1957b). Patients occasionally complain of a "stuffy nose" after nasal endotracheal intubation, and we believe that this may be due to the slow elimination of the soft paraffin remaining after the removal of the tube.

Several years ago we examined various materials to find a substitute for soft paraffin, but were unsuccessful, as no other material adhered to the tube so well. This property is particularly desirable with intranasal tubes, and all other lubricants are wiped off when passing the tube through the nose. The introduction of new bases, however, has helped us to solve this problem, since certain of the polyethylene glycols appear to have all the desired properties (Davies, 1958). These substances are polymers of ethylene glycol and the degree of polymerization is related to the approximate molecular weight. They are completely soluble in water and vary in consistency from a liquid to a hard wax, the lower polymers being more fluid. A single polymer can be found to meet the general requirements for our purpose, but in practice this is best achieved by a suitable mixture. A blend we find satisfactory is polyethylene glycol 555M of the Shell Chemical Co.

The paraffins have been used in medicine for a much longer time than the polyethylene glycols, so less experience has been acquired of the toxicity of the latter. However, all the information available points to the minimal toxicity following oral and parenteral administration of the new material. Smyth et al. (1950) give the LD50 of polyethylene glycol 1500 for white rats as 44 g/kg, when administered orally, and Carpenter and Schaffer (1932) report favourably upon the use of liquid polyethylene glycol as a solvent for intramuscular and subcutaneous injections. The polyethylene glycols of high molecular weight are reported as being somewhat less toxic than those of lower molecular weight (Smith, Carpenter and Weil, 1955), but nevertheless it is the latter which are used as solvents for injections. With regard to chronic toxicity, polyethylene glycol 400 has been fed to animals for two years at a concentration of 2 per cent in the diet, with no ill-effects (Smith, Carpenter and Weil, 1955). Also, these substances are widely used in the pharmaceutical industry as water-miscible ointment bases. We have used 555M as an endotracheal lubricant in approximately 5,000 patients with no discernible ill effects, either immediate or remote. Furthermore, we have the very definite impression that the endotracheal tubes remain in good condition for a much longer period than when lubricated with soft paraffin.

Polyethylene glycol 555M can be sterilized by dry heat at 150°C for 1 hour and 1 oz. (28.4 g.) jars are available in the anaesthetic room for the lubrication of tubes. For those anaesthetists who prefer a base containing a local anaesthetic, we provide one made up to the following formula: lignocaine base, 2 parts; sterile polyethylene glycol 555M, 98 parts.

The more fluid polyethylene glycols have been used as lubricants for other tubes, as, for example, stomach tubes and catheters. A preparation of equal viscosity to liquid paraffin can easily be made by mixing 5 parts of polyethylene glycol 555M with 95 parts polyethylene glycol 300. These liquids are clean to handle and in all respects less messy than the traditional lubricants.

We would suggest that there is now no place in anaesthesia for the continued use of paraffin products as lubricants.

ACKNOWLEDGMENTS

We are indebted to Mr. C. R. McLaughlin, F.R.C.S.E., for his help in the preparation of this article; and to the East Grinstead Anaesthesia Research Trust for a small grant in aid of an extensive library search.

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BOOK REVIEW

Einfuhrung in die prä- und postoperative Wasser- und Elektrolyttherapie. By R. Dohrmann. Published by Springer-Verlag, Berlin, Gottingen, Heidelberg, 1959. Pp. 52; 33 illustrations.

This book is written as an introduction to treatment with fluid in relation to surgical operations. If the supply of such books is any guide there must be a demand for them, and of its kind this book is adequate, although for the English reader it is not likely to be preferred to Wilkinson or LeQuesne. In some ways this book concentrates more closely on the business in hand than similar works; it is only 50 pages long, and about a third of this space is given to 33 diagrams. To give an idea of the contents, the first 16 pages summarize the physiology of body-fluid, and the next ten pages the effects of operation on body-fluid. The remainder of the book is on treatment, combining some theoretical points with a good deal of detail on the solutions used and how to give them. This section, from the viewpoint of an English reader, suffers from the fact that most of the solutions described are similar to those used here, but not identical, so the directions given, which are surprisingly detailed, cannot be strictly followed. There is an excessive devotion to formulae designed to predict how much fluid should be given; and it seems to me that the particular formulae given on page 36 would considerably underestimate any deficit of sodium or chloride.

My main criticism, however, is not that the information given is wrong; but that it stresses too much the possibility of treatment by formula in a field where a more empirical approach is perhaps safer. The value of clinical observation is mentioned, but not much else is said about it.

It seems to me that there are dangers in discussing only fluid balance in relation to operation, without also dealing with other aspects of postoperative care, or with other problems of fluid balance. Within its limits, the book is a satisfactory short account in German. References are given, and the table of contents probably takes the place of an index in this short book.

D. A. K. Black

CORRESPONDENCE

THE HEAT MECHANICS OF THE WATERS CANISTER

Sir,—May I reply as briefly as possible to Dr. Dunkin's constructive, but not entirely valid, criticisms in his letter in this Journal (April 1959).

I agree that if the operating theatre temperature is very high the temperature of the inspired gases may rise as much as five degrees centigrade above body temperature, and I think that this is *more* likely to occur in this country than in tropical climes, where the operating theatre is usually air-conditioned and is, therefore, often the coolest part of the hospital.

The highest temperature recorded in my clinical cases for inspired gases was 104°F (40°C) at a theatre temperature of 73°F (23°C).

As regards the work of Clark et al. (1954) on Body Temperature in Anaesthetized Man, their measurements of gas temperatures are unhelpful because inspired and expired gas streams were not separated at any point in the to-and-fro system; therefore, unless a temperature recording apparatus of very short time constant was used (and this was not so), any temperature recorded would be a mixture of that, of the inspired and that of the expired gases. This is well illustrated in their figure 6; the temperature recorded in the inspiratory limb of the circle system was 89°F (32°C) at the Y-junction, whereas that recorded at the tip of the endotracheal catheter was 97°F (36°C).

They also state specifically: "The results of this study indicate that above this temperature" (viz. operating room wet-bulb reading of 75°F (24°C)) "body temperature tends to rise substantially during prolonged operations *regardless of the anaesthesia system*" (my italics).

My statement that "no evidence has been found to suggest that the presence of a hot canister near the patient is in any way harmful" refers to the work described in my paper, and is entirely accurate; nor have I, as I mentioned in the preamble to the paper, been able to find in the literature any good evidence of harmful effects. I agree that it would be very interesting to study ciliary movements and bronchial dynamics, and perhaps someone with access to laboratory and animal facilities will undertake this.

As regards efficiency of carbon dioxide absorption, the experimental work was controlled to ensure total absorption. In the clinical cases there was no evidence that absorption was in any way incomplete. We do, in fact, use a pot scrub routinely to eliminate channelling as recommended by Robson and Pask (1954). Another efficient method is to incorporate a spring into the canister, which produces a similar steady compression of the granules, as used by Samson (1957) in Johannesburg.

In conclusion, I feel that to criticize the carbon dioxide absorption system for the elevation of body temperature, which not infrequently occurs during surgery in hot and humid operating conditions, is comparable with driving a motor car with the radiator blind drawn up through the steaming jungles of the Amazon, and then blaming the carburettor or the exhaust system for the over-heating which will inevitably result.

J. C. AINLEY-WALKER,
Queen Elizabeth Hospital,
Birmingham

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Samson, H. H. (1956). An improved CO_2 absorber. *Lancet*, **2**, 1196.

Sir,—I should like to take this opportunity of thanking Dr. Ainley-Walker for replying to my queries concerning his work on the Waters canister. His letter has cleared up some doubtful points. The jungle simile presents an intriguing picture and, of course, I agree that the "can" is but a minor factor in heat retention.

In fairness to the balanced view presented by Clark et al. (1954) I think that the quotation

which he gives from their article may be a little out of context. It continues in the next paragraph: "Above this temperature (75°F (24°C) wet bulb) heat retention is much more frequent when the to-and-fro system is used than when the circle or non-rebreathing techniques are employed."

The time factor of their temperature recording apparatus did mean that the readings were an average between inspiration and expiration and hence even greater intratracheal temperatures may have occurred than the maximum of 108°F (42°C) quoted when using the Waters canister. It would be helpful to know what the upper limits of this figure might be.

While questioning the effects of hot gas on the trachea and bronchi I did not wish to impute the accuracy of Dr. Ainley-Walker's observations; indeed it is the common clinical experience of most of us who use the canister that the procedure is apparently quite innocuous. In view of the scarcity of literature on the subject, I thought the notion of possible benefit to the patient required some clarification as to what he had observed in this respect when the inspired gas temperature was above that of the patient. As he suggests, further investigation would be welcome.

L. J. DUNKIN,
Newcastle General Hospital,
Newcastle upon Tyne

REFERENCE

Clark, R. E., Orkin, L. R., and Rovenstine, E. A. (1954). *J. Amer. Med. Ass.*, **154**, 311.

FACULTY OF ANAESTHETISTS

in the

ROYAL COLLEGE OF SURGEONS IN IRELAND

The President, Vice-President and Council of the Royal College of Surgeons in Ireland have inaugurated a Faculty of Anaesthetists. It is proposed to hold examinations for the Fellowship of the Faculty, but in the first instance the Council will award a limited number of Fellowships to senior Anaesthetists.

The minimum requirements of applicants will be that they should be holders of the Irish D.A. and have a further five years experience since passing the examination, or comparable experience.

Persons who wish their claims to be considered should send full particulars to the Registrar, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin, before September 1, 1959.

NORMAN RAE,
Registrar.

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